Lactam-Containing Diaminoalkyl, β-Aminoacids, α-Aminoacids And Derivatives Thereof As Factor Xa Inhibitors

CROSS-REFERENCE TO RELATED APPLICATIONS

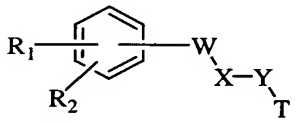
The present application claims the priority benefits of U.S. Provisional Application No. 60/415,366, filed October 2, 2002, and U.S. Provisional Application No. 60/417,208, filed October 9, 2002, all of which are expressly incorporated fully herein by reference.

FIELD OF THE INVENTION

This invention relates generally to lactam-containing diaminoalkyl, β-aminoacids, α-aminoacids and derivatives thereof which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment of thromboembolic disorders.

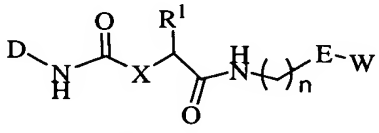
BACKGROUND OF THE INVENTION

WO02/057236 describes factor Xa inhibitors of the following formula:



wherein R_1 is selected from a small number of nitrogen containing groups, W-X form a linear core with at least one O or N, Y can be a ring, and T can be a heterocycle. WO02/057236 does not suggest or exemplify compounds like those of the present invention.

WO02/048099 describes factor Xa inhibitors of the following formula:



wherein D is phenyl or pyridyl, X is NH or O, E is phenyl or piperdinyl, and W is aryl or heterocycle. WO02/048099 does not suggest or exemplify compounds like those of the present invention.

WO02/074735 describes factor Xa inhibitors of the following formula.

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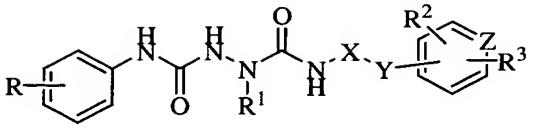
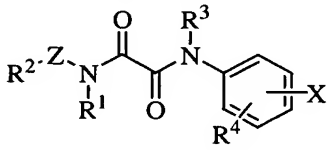


However, the present invention does not allow for four nitrogens in the linear core.

WO02/083630 describes factor Xa inhibitors of the following formula:



wherein R^2 can be aryl or heteroaryl; Z can be absent, O, N, or alkylene; and X can be aryl, aralkyl, oxo-substituted piperidine derivative, a sulfonyl, or a sulfonamide. WO02/083630 does not suggest or exemplify compounds like those of the present invention.

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, S., Varadi, K.: Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation. *Thromb. Res.* **1979**, *15*, 617-629), inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors. In addition, it is also desirable to find new compounds with improved pharmacological characteristics compared with known factor Xa inhibitors. For example, it is preferred to find new compounds with improved factor Xa inhibitory activity and selectivity for factor Xa versus other serine proteases (i.e., trypsin). It is also desirable and preferable to find compounds with advantageous and improved characteristics in one or more of the following categories, but are not limited to: (a) pharmaceutical properties (e.g., solubility, permeability, and amenability to sustained release formulations); (b) dosage

requirements (e.g., lower dosages and/or once-daily dosing); (c) factors which decrease blood concentration peak-to-trough characteristics (e.g., clearance and/or volume of distribution); (d) factors that increase the concentration of active drug at the receptor (e.g., protein binding, volume of distribution); (e) factors that decrease the liability for clinical drug-drug interactions (e.g., cytochrome P450 enzyme inhibition or induction); (f) factors that decrease the potential for adverse side-effects (e.g., pharmacological selectivity beyond serine proteases, potential chemical or metabolic reactivity, and limited CNS penetration); and, (g) factors that improve manufacturing costs or feasibility (e.g., difficulty of synthesis, number of chiral centers, chemical stability, and ease of handling).

SUMMARY OF THE INVENTION

Accordingly, the present invention provides novel lactam-containing ethylene diamine, β-aminoacids, α-aminoacids and derivatives thereof that are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

The present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides a novel method of treating a patient in need of thromboembolic disorder treatment, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a thromboembolic disorder.

The present invention provides a novel method, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a thromboembolic disorder.

The present invention provides novel lactam-containing compounds and derivatives thereof for use in therapy.

The present invention provides the use of novel lactam-containing compounds for the manufacture of a medicament for the treatment of a thromboembolic disorder.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that lactam-containing ethylene diamine, β-aminoacids, and α-aminoacids compounds of Formula I:

$$P\text{-}M\text{-}M_1$$

I

wherein P, M, and M_1 are defined below, or pharmaceutically acceptable salt or prodrug forms thereof, are effective factor Xa inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] In an embodiment, the present invention provides a novel compound of formula I:

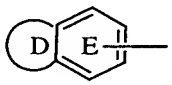
$$P\text{-}M\text{-}M_1$$

I

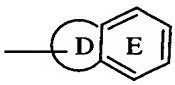
or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

one of P and M_1 is –G and the other -A-B;

G is a group of formula IIa or IIb:



IIa



IIb

ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered ring consisting of: carbon atoms and 0-3 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

ring D is substituted with 0-2 R, 0-2 carbonyls, and there are 0-3 ring double bonds;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 1-2 R;

alternatively, ring D is absent and ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thienyl, and thiazolyl, and ring E is substituted with 1-2 R;

alternatively, ring D is absent and ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thienyl, and thiazolyl, and ring E is substituted with 1 R and with a 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, wherein the 5-6 membered heterocycle is substituted with 0-1 carbonyls and 1-2 R and there are 0-3 ring double bonds;

R is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, -CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $ONHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $(CR^8R^9)_tC(O)H$, $(CR^8R^9)_tC(O)R^{2c}$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, $(CR^8R^9)_tNR^7C(O)R^7$, $(CR^8R^9)_tOR^3$, $(CR^8R^9)_tS(O)_pNR^7R^8$, $(CR^8R^9)_tNR^7S(O)_pR^7$, $(CR^8R^9)_tSR^3$, $(CR^8R^9)_tS(O)R^3$, $(CR^8R^9)_tS(O)_2R^3$, and OCF_3;

alternatively, when 2 R groups are attached to adjacent atoms, they combine to form methylenedioxy or ethylenedioxy;

M is 3-8 membered linear chain consisting of: carbon atoms, 0-3 carbonyl groups, 0-1 thiocarbonyl groups, and 1-3 heteroatoms selected from O, N, and $S(O)_p$, and M is substituted with 0-3 R^{1a} and 0-2 R^2, and there are 0-2 double bonds and 0-1 triple bond; provided that other than an S-S, S-O, or O-O bond is present in M;

provided that linker M comprises other than a N-C(O)-C(O)-N group;

further provided that one or more of the following apply:

(a) if linker M comprises a ureido-methylene-carbonyl-amino or carbamoyloxy-methylene-carbonyl-amino group, then ring D is present or ring E is other than phenyl or pyridyl;

(b) there is at least one $S(O)_p$ group present in linker M;

(c) there are at least two carbonyl groups present in linker M;

(d) ring D is present in group G;

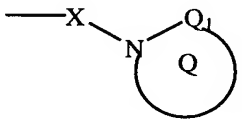
(e) ring E is other than phenyl; and

(f) if ring D is absent and ring E is phenyl, then R is other than CN, $C(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $(CR^8R^9)_tNR^7R^8$, and $(CR^8R^9)_tC(O)NR^7R^8$;

A is selected from:

C_{3-10} carbocycle substituted with 0-2 R^4, and

5-12 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^4;

B is 

; provided that Z and B are attached to different atoms on A and that the A-X-N moiety forms other than a N-N-N group;

Q_1 is selected from C=O and SO_2;

ring Q is a 4-8 membered monocyclic or bicyclic ring consisting of, in addition to the N-Q_1 group shown, carbon atoms and 0-2 heteroatoms selected from NR^{4c}, O, S, S(O), and $S(O)_2$, wherein:

0-2 double bonds are present within the ring and the ring is substituted with 0-2 R^{4a};

alternatively, ring Q is a 4-8 membered monocyclic or bicyclic ring to which another ring is fused, wherein:

the 4-7 membered ring consists of, in addition to the shown amide group, carbon atoms and 0-2 heteroatoms selected from NR^{4c}, O, S, S(O), and $S(O)_2$ and 0-2 double bonds are present within the ring;

the fusion ring is phenyl or a 5-6 membered heteroaromatic consisting of carbon atoms and 1-2 heteroatoms selected from NR^{4c}, O, S, S(O), and $S(O)_2$;

ring Q, which includes the 4-7 membered ring and the fusion ring, is substituted with 0-3 R^{4a};

alternatively, two non-adjacent atoms of one of the rings of ring Q are bridged with 1-2 atoms selected from: carbon atoms, NR^{4c}, O, S, S(O), and $S(O)_2$, provided bonds other than O-O, $S(O)_p$-O, $S(O)_p$-$S(O)_p$, N-O, and N-$S(O)_p$ are present;

X is absent or is selected from $-(CR^2R^{2a})_{1-4}$-, $-CR^2(CR^2R^{2b})(CH_2)_t$-, -C(O)-, $-C(=NR^{1c})$-, $-CR^2(NR^{1c}R^2)$-, $-CR^2(OR^2)$-, $-CR^2(SR^2)$-, $-C(O)CR^2R^{2a}$-, $-CR^2R^{2a}C(O)$, -S(O)-, $-S(O)_2$-, $-SCR^2R^{2a}$-, $-S(O)CR^2R^{2a}$-, $-S(O)_2CR^2R^{2a}$-, $-CR^2R^{2a}S(O)$-, $-CR^2R^{2a}S(O)_2$-, $-S(O)_2NR^2CR^2R^{2a}$-, $--NR^2S(O)_2$-, $-CR^2R^{2a}NR^2S(O)_2$-, $-NR^2S(O)_2CR^2R^{2a}$-, $-NR^2C(O)$-, $-C(O)NR^2CR^2R^{2a}$-, $-NR^2C(O)CR^2R^{2a}$-, $-CR^2R^{2a}NR^2C(O)$-, $-NR^2CR^2R^{2a}$-, and $-OCR^2R^{2a}$-;

R^{1a}, at each occurrence, is selected from H, $-(CR^3R^{3a})_r$-R^{1b}, $-(CR^3R^{3a})_r$-$CR^3R^{1b}R^{1b}$, $-(CR^3R^{3a})_r$-O-$(CR^3R^{3a})_r$-R^{1b}, $-C_{2-6}$ alkenylene-R^{1b}, $-C_{2-6}$ alkynylene-R^{1b}, $-(CR^3R^{3a})_r$-$C(=NR^{1b})NR^3R^{1b}$, $NR^3(CR^3R^{3a})_tR^{1c}$, $O(CR^3R^{3a})_tR^{1c}$, $(CR^3R^{3a})_rSCR^3R^{3a}R^{1c}$, $(CR^3R^{3a})_rNR^3(CR^3R^{3a})_rR^{1b}$, $(CR^3R^{3a})_rC(O)NR^2(CR^3R^{3a})_rR^{1b}$, $CO_2(CR^3R^{3a})_tR^{1b}$, $O(CR^3R^{3a})_tR^{1b}$,

$(CR^3R^{3a})_rS(CR^3R^{3a})_rR^{1b}$, $S(O)_p(CR^3R^{3a})_rR^{1d}$, $O(CR^3R^{3a})_rR^{1d}$, $NR^3(CR^3R^{3a})_rR^{1d}$, $OC(O)NR^3(CR^3R^{3a})_rR^{1d}$, $NR^3C(O)NR^3(CR^3R^{3a})_rR^{1d}$, $NR^3C(O)O(CR^3R^{3a})_rR^{1d}$, and $NR^3C(O)(CR^3R^{3a})_rR^{1d}$, provided that R^{1a} forms other than an N-halo, N-S, O-O, or N-CN bond;

alternatively, when two R^{1a} groups are attached to the same carbon atom, together with the carbon atom to which they are attached they form a 3-10 membered carbocyclic or heterocyclic ring consisting of: carbon atoms and 0-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^4 and 0-3 ring double bonds;

R^{1b} is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, $-NO_2$, -CHO, $(CF_2)_rCF_3$, $(CR^3R^{3a})_rOR^2$, NR^2R^{2a}, $C(O)R^{2b}$, CO_2R^{2b}, $OC(O)R^2$, $(CF_2)_rCO_2R^{2a}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $C(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^2R^{2a}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2R^2$, $C(O)NR^2SO_2R^2$, $SO_2R^2C(O)NR^2$, $SO_2NR^2C(O)R^2$, C_{3-10} carbocycle substituted with 0-2 R^4, and 4-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^4, provided that R^{1b} forms other than an O-O, N-halo, N-S, or N-CN bond;

R^{1c} is selected from H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^2$, $S(O)_2R^2$, and $SO_2NR^2R^{2a}$;

R^{1d} is selected from C_{3-6} carbocycle substituted with 0-2 R^{4b} and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b}, provided that R^{1d} forms other than an N-S bond;

R^2, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5-8 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy substituted with 0-2 R^{4b}, C_{1-6} alkyl substituted with 0-2 R^{4b}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^3, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, and phenyl;

alternatively, R^3 and R^{3a}, together with the nitrogen atom to which they are attached, combine to form a 5 or 6 membered saturated, partially unsaturated, or unsaturated ring consisting of: carbon atoms, the nitrogen atom to which R^3 and R^{3a} are attached, and 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{3c}, at each occurrence, is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, and phenyl;

R^{3d}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, C_{1-4} alkyl-phenyl, and $C(=O)R^{3c}$;

R^4, at each occurrence, is selected from H, =O, $(CR^3R^{3a})_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, $(CR^3R^{3a})_rCN$, $(CR^3R^{3a})_rNO_2$, $(CR^3R^{3a})_rNR^2R^{2a}$, $(CR^3R^{3a})_rC(O)R^{2c}$, $(CR^3R^{3a})_rNR^2C(O)R^{2b}$, $(CR^3R^{3a})_rC(O)NR^2R^{2a}$, $(CR^3R^{3a})_rNR^3(CR^3R^{3a})_rC(O)NR^3R^{3a}$, $(CR^3R^{3a})_rNR^3(CR^3R^{3a})_rC(O)OR^3$, $(CR^3R^{3a})_rNR^3(CR^3R^{3a})_rNR^3R^{3a}$, $(CR^3R^{3a})_rNR^3(CR^3R^{3a})_rNR^3C(O)R^{3a}$, $(CR^3R^{3a})_rNR^3(CR^3R^{3a})_rNR^3SO_2R^{3a}$, $(CR^3R^{3a})_rNR^2C(O)NR^2R^{2a}$, $(CR^3R^{3a})_rC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rC(=NS(O)_2R^5)NR^2R^{2a}$, $(CR^3R^{3a})_rNHC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rC(O)NHC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rSO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2$-C_{1-4} alkyl, $(CR^3R^{3a})_rNR^2SO_2R^5$, $(CR^3R^{3a})_rS(O)_pR^{5a}$, $(CR^3R^{3a})_r(CF_2)_rCF_3$, $NHCH_2R^{1c}$, OCH_2R^{1c}, SCH_2R^{1c}, $NH(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, $(CR^3R^{3a})_r$-3-10 membered carbocycle substituted with 0-

1 R^5, and a $(CR^3R^{3a})_r$-5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, $(CR^3R^{3a})_rOR^2$, $(CR^3R^{3a})_rF$, $(CR^3R^{3a})_rBr$, $(CR^3R^{3a})_rCl$, C_{1-4} alkyl, $(CR^3R^{3a})_rCN$, $(CR^3R^{3a})_rNO_2$, $(CR^3R^{3a})_rNR^2R^{2a}$, $(CR^3R^{3a})_rC(O)R^{2c}$, $(CR^3R^{3a})_rNR^2C(O)R^{2b}$, $(CR^3R^{3a})_rC(O)NR^2R^{2a}$, $(CR^3R^{3a})_rN=CHOR^3$, $(CR^3R^{3a})_rC(O)NH(CH_2)_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2C(O)NR^2R^{2a}$, $(CR^3R^{3a})_rC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rNHC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rSO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2$-C_{1-4} alkyl, $(CR^3R^{3a})_rC(O)NHSO_2$-C_{1-4} alkyl, $(CR^3R^{3a})NR^2SO_2R^5$, $(CR^3R^{3a})_rS(O)_pR^{5a}$, $(CR^3R^{3a})_r(CF_2)_rCF_3$, $(CR^3R^{3a})_r$-5-6 membered carbocycle substituted with 0-1 R^5, and a $(CR^3R^{3a})_r$-5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, $(CH_2)_rF$, $(CH_2)_rCl$, $(CH_2)_rBr$, $(CH_2)_rI$, C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $(CH_2)_rNR^3C(O)R^{3a}$, $(CH_2)_r$-$C(O)NR^3R^{3a}$, $(CH_2)_rNR^3C(O)NR^3R^{3a}$, $(CH_2)_rC(=NR^3)NR^3R^{3a}$, $(CH_2)_rNR^3C(=NR^3)NR^3R^{3a}$, $(CH_2)_rSO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2$-C_{1-4} alkyl, $(CH_2)_rNR^3SO_2CF_3$,$(CH_2)_rNR^3SO_2$-phenyl, $(CH_2)_rS(O)_pCF_3$, $(CH_2)_rS(O)_p$-C_{1-4} alkyl, $(CH_2)_rS(O)_p$-phenyl, $(CH_2)_r(CF_2)_rCF_3$, $(CH_2)_r$-3-10 membered carbocycle substituted with 0-1 R^3, and a $(CH_2)_r$-5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^3;

R^{4c}, at each occurrence, is selected from H, C_{1-4} alkyl $(CR^3R^{3a})_{r1}OR^2$, $(CR^3R^{3a})_{r1}F$, $(CR^3R^{3a})_{r1}Br$, $(CR^3R^{3a})_{r1}Cl$, $(CR^3R^{3a})_{r1}CN$, $(CR^3R^{3a})_{r1}NO_2$, $(CR^3R^{3a})_{r1}NR^2R^{2a}$, $(CR^3R^{3a})_rC(O)R^{2c}$, $(CR^3R^{3a})_{r1}NR^2C(O)R^{2b}$, $(CR^3R^{3a})_rC(O)NR^2R^{2a}$, $(CR^3R^{3a})_{r1}N{=}CHOR^3$, $(CR^3R^{3a})_rC(O)NH(CH_2)_2NR^2R^{2a}$, $(CR^3R^{3a})_{r1}NR^2C(O)NR^2R^{2a}$, $(CR^3R^{3a})_{r1}C(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_{r1}NHC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rSO_2NR^2R^{2a}$, $(CR^3R^{3a})_{r1}NR^2SO_2NR^2R^{2a}$, $(CR^3R^{3a})_{r1}NR^2SO_2$-$C_{1-4}$ alkyl, $(CR^3R^{3a})_rC(O)NHSO_2$-C_{1-4} alkyl, $(CR^3R^{3a})_{r1}NR^2SO_2R^5$, $(CR^3R^{3a})_rS(O)_pR^{5a}$, $(CR^3R^{3a})_r(CF_2)_rCF_3$, $(CR^3R^{3a})_r$-5-6 membered carbocycle substituted with 0-1 R^5, and a $(CR^3R^{3a})_r$-5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

R^5, at each occurrence, is selected from H, C_{1-6} alkyl, =O, $(CH_2)_rOR^3$, F, Cl, Br, I, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $(CH_2)_rNR^3C(O)R^{3a}$, $(CH_2)_rC(O)NR^3R^{3a}$, $(CH_2)_rNR^3C(O)NR^3R^{3a}$, $(CH_2)_rCH(=NOR^{3d})$, $(CH_2)_rC(=NR^3)NR^3R^{3a}$, $(CH_2)_rNR^3C(=NR^3)NR^3R^{3a}$, $(CH_2)_rSO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2$-C_{1-4} alkyl, $(CH_2)_rNR^3SO_2CF_3$, $(CH_2)_rNR^3SO_2$-phenyl, $(CH_2)_rS(O)_pCF_3$, $(CH_2)_rS(O)_p$-C_{1-4} alkyl, $(CH_2)_rS(O)_p$-phenyl, $(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^{5a}, at each occurrence, is selected from C_{1-6} alkyl, $(CH_2)_rOR^3$, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $(CH_2)_rNR^3C(O)R^{3a}$, $(CH_2)_rC(O)NR^3R^{3a}$, $(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6, provided that R^{5a} does not form a S-N or $S(O)_p$-C(O) bond;

R^6, at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and NR^2SO_2-C_{1-4} alkyl;

R^7, at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkyl-C(O)-, C_{1-6} alkyl-O-, $(CH_2)_n$-phenyl, C_{1-6} alkyl-OC(O)-, C_{6-10} aryl-O-, C_{6-10} aryl-OC(O)-, C_{6-10} aryl-CH_2-C(O)-, C_{1-4} alkyl-C(O)O-C_{1-4} alkyl-OC(O)-, C_{6-10} aryl-C(O)O-C_{1-4} alkyl-OC(O)-, C_{1-6} alkyl-NH_2-C(O)-, phenyl-NH_2-C(O)-, and phenyl C_{0-4} alkyl-C(O)-;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl, and $(CH_2)_n$-phenyl;

alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5-10 membered heterocyclic ring consisting of carbon atoms and 0-2 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^9, at each occurrence, is selected from H, C_{1-6} alkyl, and $(CH_2)_n$-phenyl;

n, at each occurrence, is selected from 0, 1, 2, and 3;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, 4, 5, and 6;

r1, at each occurrence, is selected from 1, 2, 3, 4, 5, and 6; and

t, at each occurrence, is selected from 0, 1, 2, and 3.

Preferably, when proviso (d) applies, then ring D is 5-membered and attached directly to M.

Preferably, when proviso (e) applies, then ring E is attached to M.

Preferably, M has 1-3 N and (a) 1 $S(O)_p$, (b) 2-3 carbonyl groups, or (c) a combination of of (a) and (b).

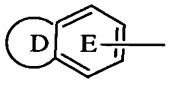
Preferably, M is attached to G via -S(O)p, -C(O), or -NHC(O).

[2] In another preferred embodiment, the present invention provides a novel compound, wherein:

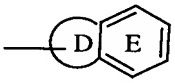
one of P and M_1 is -G and the other -A-B;

M is 3-8 membered linear chain consisting of: carbon atoms, 1-3 carbonyl groups, 0-1 thiocarbonyl groups, and 1-3 heteroatoms selected from O, $S(O)_p$, and N, and M is substituted with 0-3 R^{1a} and 0-2 R^2 and there are 0-1 double bonds, provided that other than an S-S, S-O, or O-O bond is present in M;

G is a group of formula IIa or IIb:



IIa



IIb

ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

ring D is substituted with 0-2 R and there are 0-3 ring double bonds;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 1-2 R;

alternatively, ring D is absent, and ring E is selected from phenyl, pyridyl, pyridazinyl, pyrimidyl, and thienyl, and ring E is substituted with 1-2 R;

alternatively, ring D is absent, ring E is selected from phenyl, pyridyl, and thienyl, and ring E is substituted with 1 R and with a 5 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, wherein the 5 membered heterocycle is substituted with 0-1 carbonyls and 1-2 R and there are 0-3 ring double bonds;

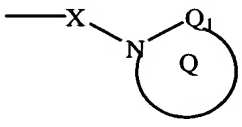
R is selected from H, C_{1-4} alkyl, F, Cl, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, CN, $C(=NH)NH_2$, $C(=NH)NHOH$, $C(=NH)NHOCH_3$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $(CR^8R^9)_tNR^7R^8$, $C(O)NR^7R^8$, $CH_2C(O)NR^7R^8$, $S(O)_2R^3$, $S(O)_pNR^7R^8$, $CH_2S(O)_pNR^7R^8$, and OCF_3;

alternatively, when 2 R groups are attached to adjacent atoms, they combine to form methylenedioxy or ethylenedioxy;

A is selected from:

C_{5-10} carbocycle substituted with 0-2 R^4, and

5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^4;

B is 

; provided that Z and B are attached to different atoms on A and that the A-X-N moiety forms other than a N-N-N group;

ring Q is a 4-7 membered monocyclic or tricyclic ring consisting of, in addition to the N-Q_1 group shown, carbon atoms and 0-2 heteroatoms selected from NR^{4c}, O, S, S(O), and $S(O)_2$, wherein:

0-2 double bonds are present within the ring and the ring is substituted with 0-2 R^{4a};

alternatively, ring Q is a 4-7 membered ring to which another ring is fused, wherein:

the 4-7 membered ring consists of, in addition to the shown amide group, carbon atoms and 0-2 heteroatoms selected from NR^{4c}, O, S, S(O), and $S(O)_2$ and 0-1 double bonds are present within the ring;

the fusion ring is phenyl or a 5-6 membered heteroaromatic consisting of carbon atoms and 1-2 heteroatoms selected from NR^{4c}, O, and S;

ring Q, which includes the 4-7 membered ring and the fusion ring, is substituted with 0-3 R^{4a};

X is absent or is selected from $-(CR^2R^{2a})_{1-4}$-, -C(O)-, $-C(O)CR^2R^{2a}$-, $-CR^2R^{2a}C(O)$, $-S(O)_2$-, $-S(O)_2CR^2R^{2a}$-, $-CR^2R^{2a}S(O)_2$-, $-NR^2S(O)_2$-, $-NR^2CR^2R^{2a}$-, and $-OCR^2R^{2a}$-;

R^{1a}, at each occurrence, is selected from H, $-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-O-(CR^3R^{3a})_r-R^{1b}$, $-C_{2-6}$ alkenylene-R^{1b}, $-C_{2-6}$ alkynylene-R^{1b}, $-(CR^3R^{3a})_r-C(=NR^{1b})NR^3R^{1b}$, $NR^3(CR^3R^{3a})_tR^{1c}$, $O(CR^3R^{3a})_tR^{1c}$, $(CR^3R^{3a})_rSCR^3R^{3a}R^{1c}$, $(CR^3R^{3a})_rNR^3(CR^3R^{3a})_rR^{1b}$, $(CR^3R^{3a})_rC(O)NR^2(CR^3R^{3a})_rR^{1b}$, $CO_2(CR^3R^{3a})_tR^{1b}$, $O(CR^3R^{3a})_tR^{1b}$, $S(O)_p(CR^3R^{3a})_rR^{1d}$, $O(CR^3R^{3a})_rR^{1d}$, $NR^3(CR^3R^{3a})_rR^{1d}$, $OC(O)NR^3(CR^3R^{3a})_rR^{1d}$, $NR^3C(O)NR^3(CR^3R^{3a})_rR^{1d}$, $NR^3C(O)O(CR^3R^{3a})_rR^{1d}$, and $NR^3C(O)(CR^3R^{3a})_rR^{1d}$, provided that R^{1a} forms other than an N-halo, N-S, O-O, or N-CN bond;

alternatively, when two R^{1a} groups are attached to the same carbon atom, together with the carbon atom to which they are attached they form a 3-10 membered carbocyclic or heterocyclic ring consisting of: carbon atoms and 0-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^4 and 0-3 ring double bonds;

R^{1b} is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, F, Cl, Br, I, -CN, -CHO, CF_3, $(CR^3R^{3a})_rOR^2$, NR^2R^{2a}, $C(O)R^{2b}$, CO_2R^{2b}, $OC(O)R^2$, CO_2R^{2a}, $S(O)_pR^2$, $NR^2(CH_2)_rOR^2$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^2R^{2a}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2R^2$, $C(O)NR^2SO_2R^2$, $SO_2NR^2C(O)R^2$, C_{3-10} carbocycle substituted with 0-2 R^4, and 4-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^4, provided that R^{1b} forms other than an O-O, N-halo, N-S, or N-CN bond;

R^{1c} is selected from H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^2$, $S(O)_2R^2$, and $SO_2NR^2R^{2a}$;

R^2, at each occurrence, is selected from H, CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{5-6} carbocycle substituted with 0-2 R^{4b}, a C_{5-6} carbocyclic-CH_2- group substituted with 0-2 R^{4b}, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{5-6} carbocycle substituted with 0-2 R^{4b}, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring

substituted with 0-2 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{5-6} carbocycle substituted with 0-2 R^{4b}, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{5-6} carbocycle substituted with 0-2 R^{4b}, and 5-6 membered heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^3, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, and phenyl;

alternatively, R^3 and R^{3a}, together with the nitrogen atom to which they are attached, combine to form a 5 or 6 membered saturated, partially unsaturated, or unsaturated ring consisting of: carbon atoms and the nitrogen atom to which R^3 and R^{3a} are attached;

R^{3c}, at each occurrence, is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, and phenyl;

R^{3d}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2-phenyl, CH_2CH_2-phenyl, and $C(=O)R^{3c}$;

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $(CH_2)_rNR^2C(O)R^{2b}$, $(CH_2)_rC(O)NR^2R^{2a}$, $(CH_2)_rNR^3(CH_2)_{1-4}C(O)NR^3R^{3a}$, $(CH_2)_rNR^3(CH_2)_{1-4}C(O)OR^3$, $(CH_2)_rNR^3(CH_2)_{1-4}NR^3R^{3a}$, $(CH_2)_rNR^3(CH_2)_{1-4}NR^3C(O)R^{3a}$, $(CH_2)_rNR^3(CH_2)_{1-4}NR^3SO_2R^{3a}$, $(CH_2)_rNR^2C(O)NR^2R^{2a}$, $(CH_2)_rC(=NR^2)NR^2R^{2a}$, $(CH_2)_rNHC(=NR^2)NR^2R^{2a}$, $(CH_2)_rSO_2NR^2R^{2a}$, $(CH_2)_rNR^2SO_2NR^2R^{2a}$, $(CH_2)_rNR^2SO_2$-C_{1-4} alkyl, $(CH_2)_rNR^2SO_2R^5$, $(CH_2)_rS(O)_pR^{5a}$, $(CH_2)_rCF_3$, $(CH_2)_r$-3-7 membered carbocycle substituted with 0-1 R^5, and a $(CH_2)_r$-5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, CH_2OR^2, OR^2, CH_2F, F, CH_2Br, Br, CH_2Cl, Cl, C_{1-4} alkyl, CH_2-CN, -CN, CH_2NO_2, NO_2, $CH_2NR^2R^{2a}$, NR^2R^{2a}, CH_2-$C(O)R^{2c}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $(CH_2)_rC(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $(CH_2)_rSO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $(CH_2)_rS(O)_pR^{5a}$, CH_2CF_3, CF_3, CH_2-5-6 membered carbocycle substituted with 0-1 R^5, 5-6 membered carbocycle substituted with 0-1 R^5, and a CH_2-5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

R^{4b}, at each occurrence, is selected from H, =O, OR^3, $(CH_2)_rOR^3$, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $(CH_2)_rNR^3C(O)R^{3a}$, $(CH_2)_rC(O)NR^3R^{3a}$, $(CH_2)_rNR^3C(O)NR^3R^{3a}$, $(CH_2)_rC(=NR^3)NR^3R^{3a}$, $(CH_2)_rNR^3C(=NR^3)NR^3R^{3a}$, $(CH_2)_rSO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2$-C_{1-4} alkyl, $(CH_2)_rNR^3SO_2CF_3$, $(CH_2)_rNR^3SO_2$-phenyl, $(CH_2)_rS(O)_pCF_3$, $(CH_2)_rS(O)_p$-C_{1-4} alkyl, $(CH_2)_rS(O)_p$-phenyl, and $(CH_2)_rCF_3$;

R^{4c}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, CH_2OR^2, CH_2F, CH_2Br, CH_2Cl, CH_2CN, CH_2NO_2, $CH_2NR^2R^{2a}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $CH_2NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $CH_2C(O)NR^2R^{2a}$, $CH_2NR^2C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $CH_2SO_2NR^2R^{2a}$, $CH_2NR^2SO_2NR^2R^{2a}$, $CH_2NR^2SO_2$-C_{1-4} alkyl, $C(O)NHSO_2$-C_{1-4} alkyl, $CH_2C(O)NHSO_2$-C_{1-4} alkyl, $CH_2NR^2SO_2R^5$, $S(O)_pR^{5a}$, $CH_2S(O)_pR^{5a}$, CF_3, CH_2CF_3, 5-6 membered carbocycle substituted with 0-1 R^5, $CH_2$5-6 membered carbocycle substituted with 0-1 R^5, 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5, and a $CH_2$5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

R^5, at each occurrence, is selected from H, =O, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, OR^3, CH_2OR^3, F, Cl, -CN, NO_2, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, $CH_2C(O)R^3$, $C(O)OR^{3c}$, $CH_2C(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NOR^{3d})$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$,

$SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, CF_3, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

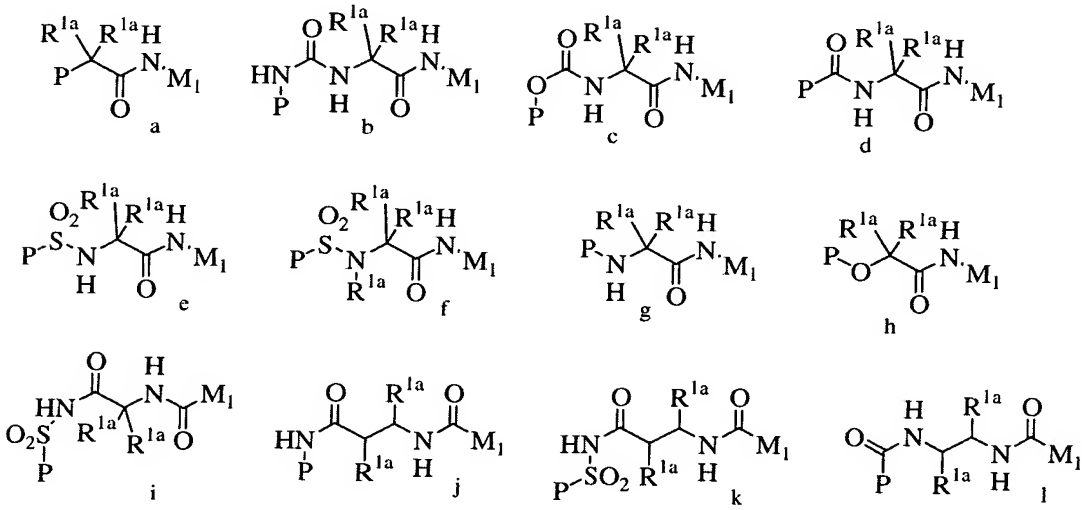
R^6, at each occurrence, is selected from H, OH, OR^2, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, -CN, NO_2, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2b}$, $CH_2C(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

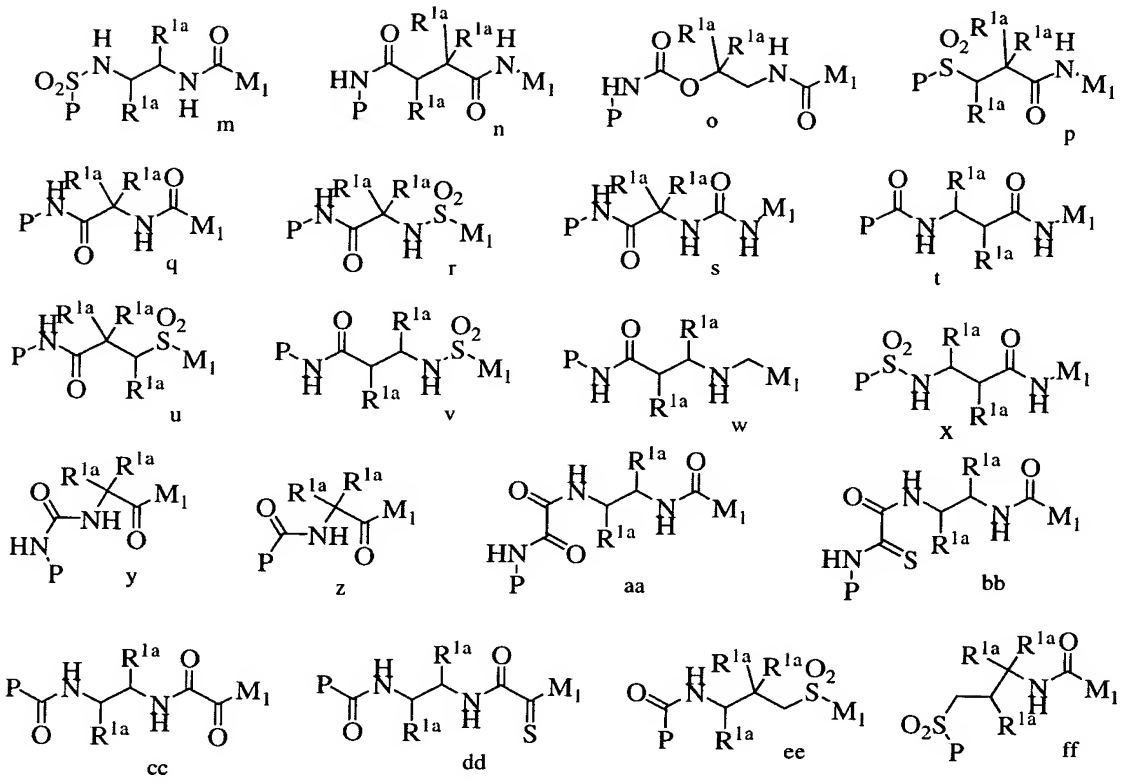
r, at each occurrence, is selected from 0, 1, 2, and 3;

r1, at each occurrence, is selected from 1, 2, and 3; and

t, at each occurrence, is selected from 0, 1, and 2.

[3] In another preferred embodiment, the present invention provides a novel compound selected from compounds a-ff:

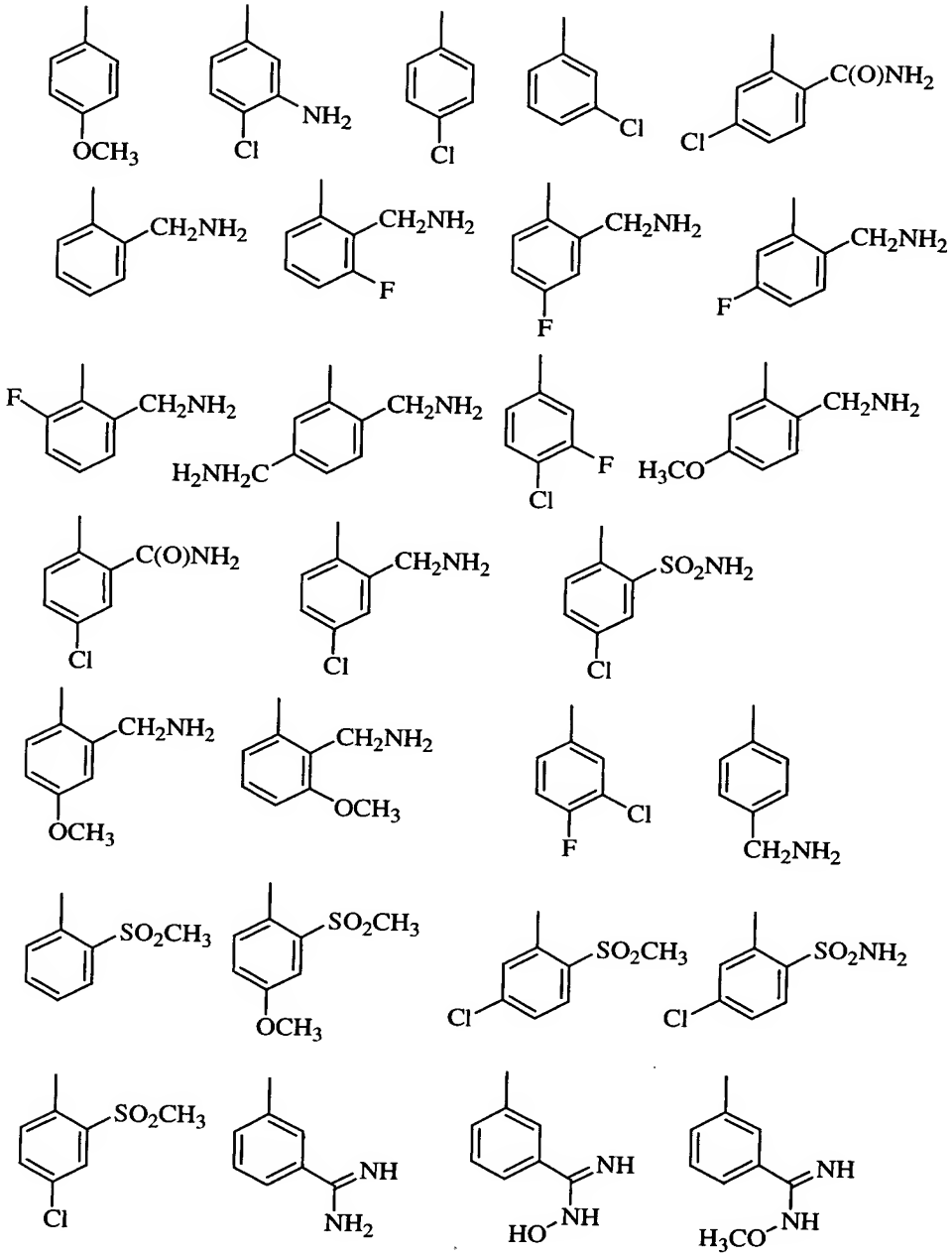


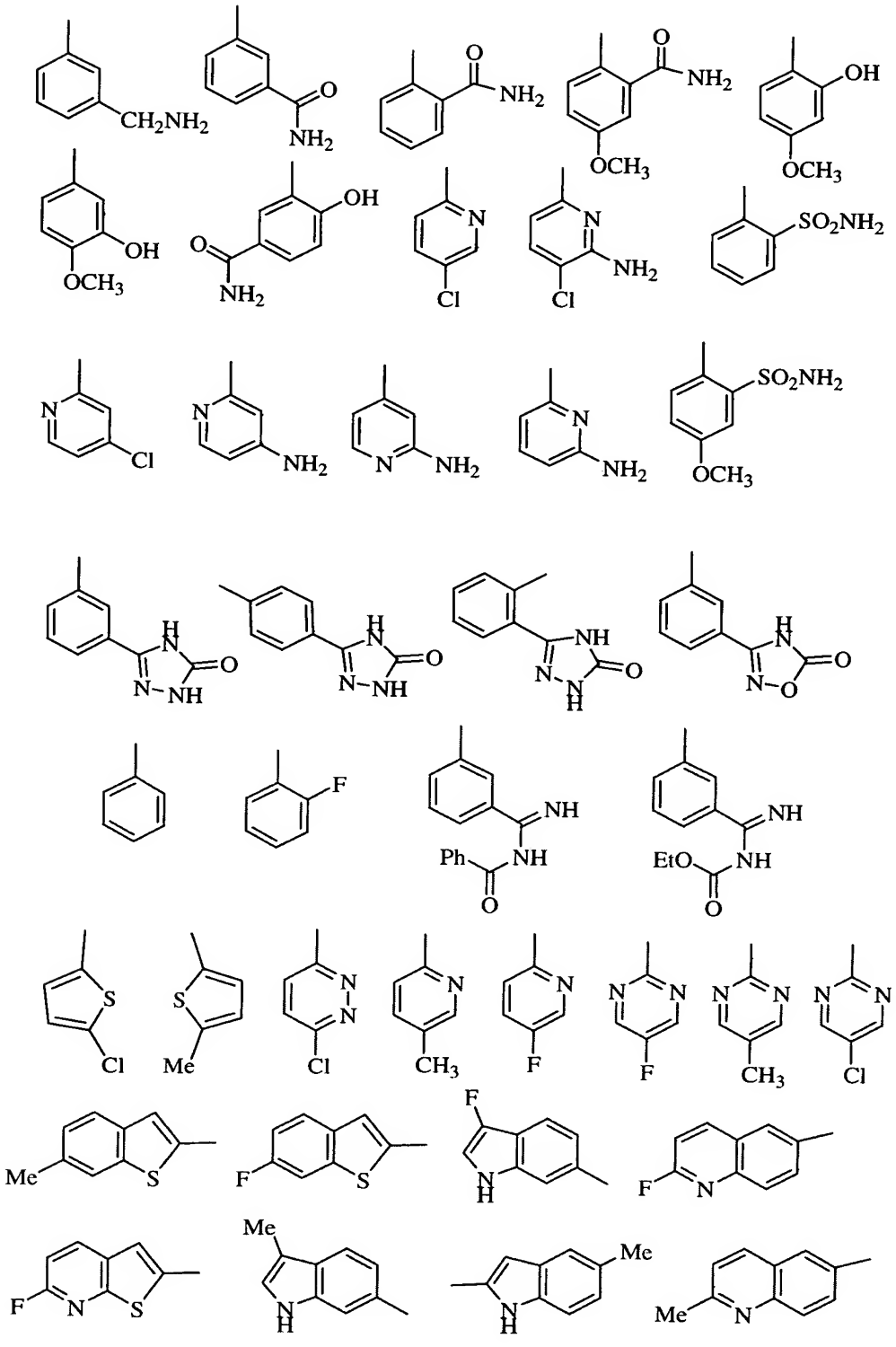


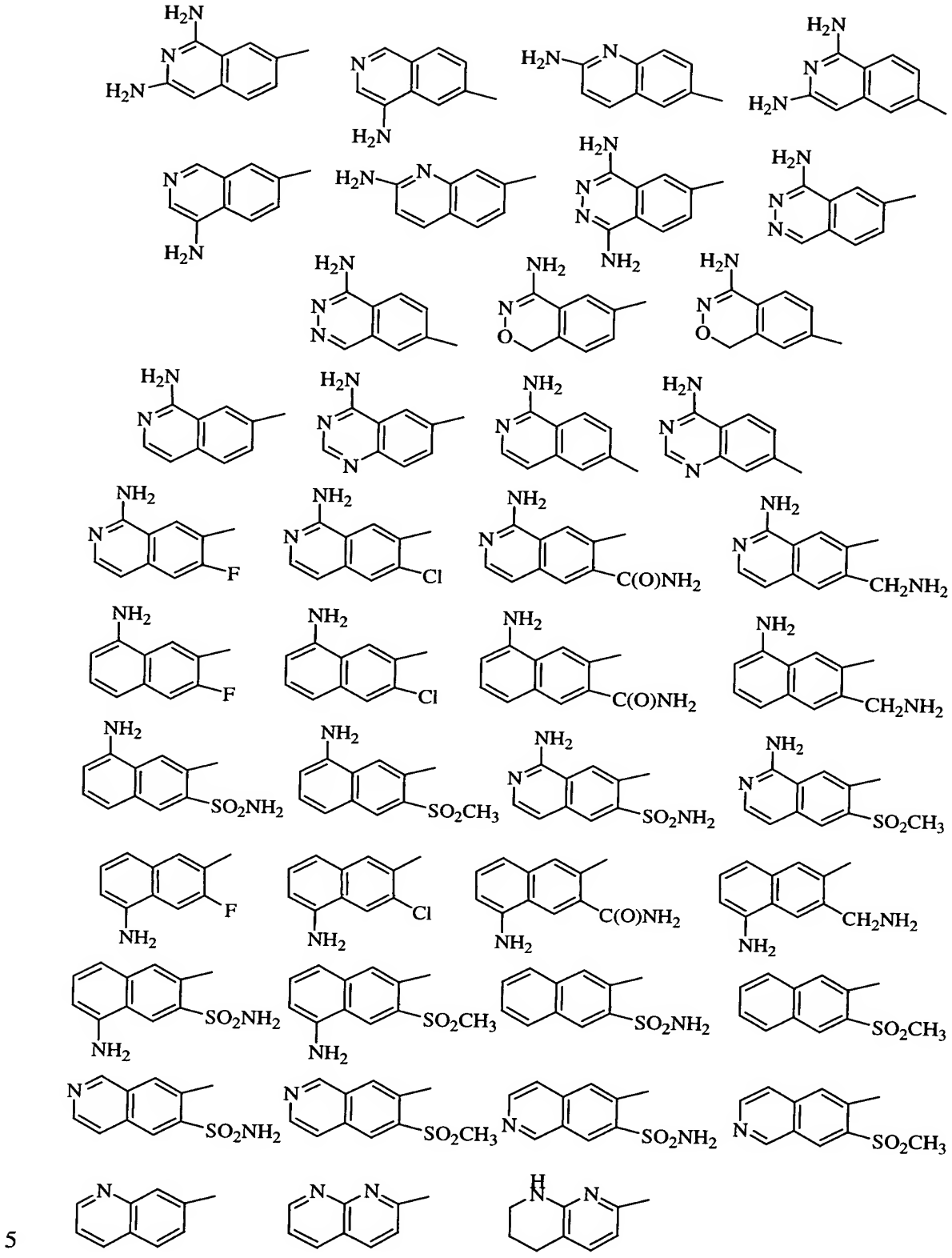
wherein:

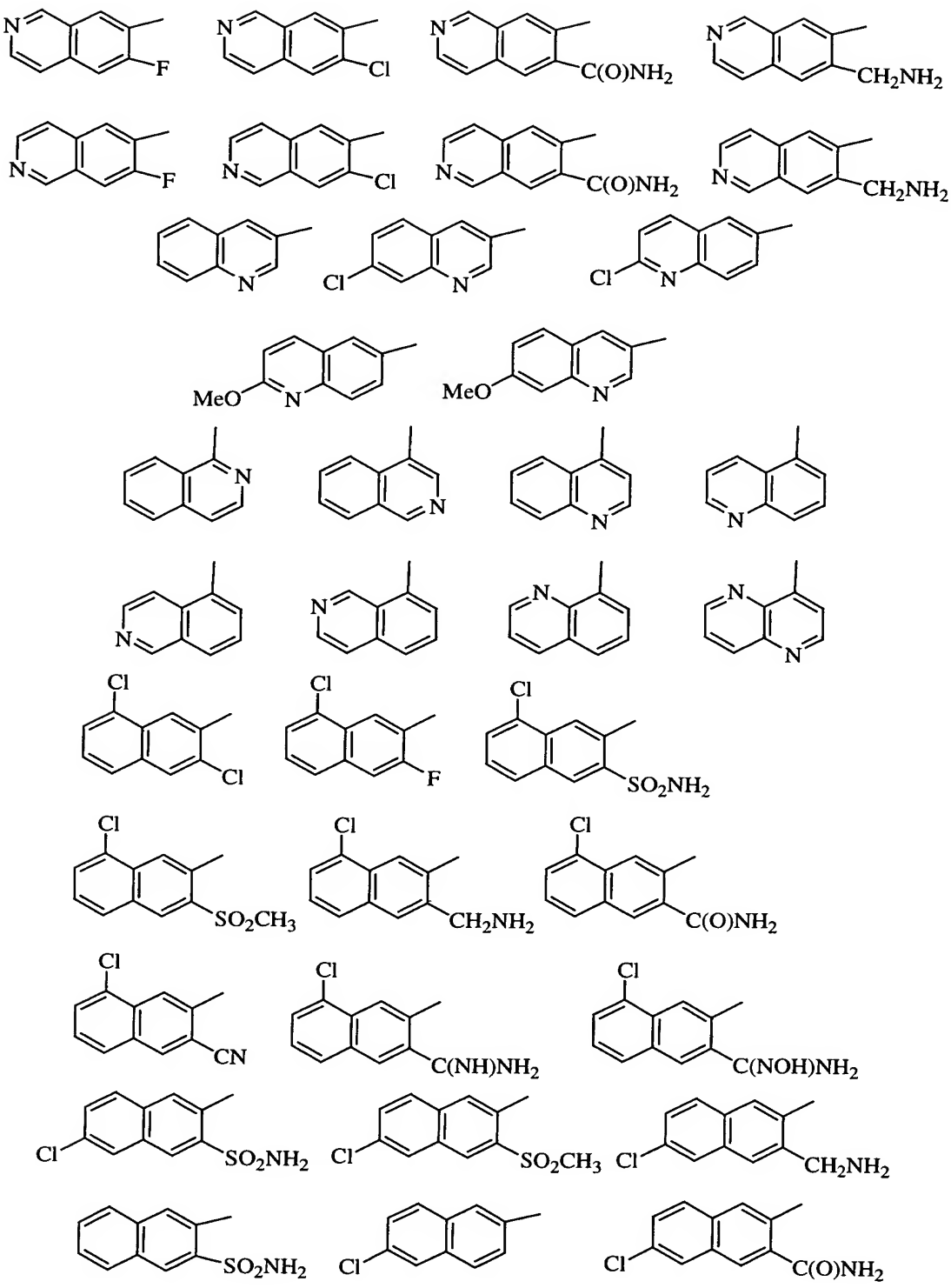
one of P and M_1 is -G and the other -A-B;

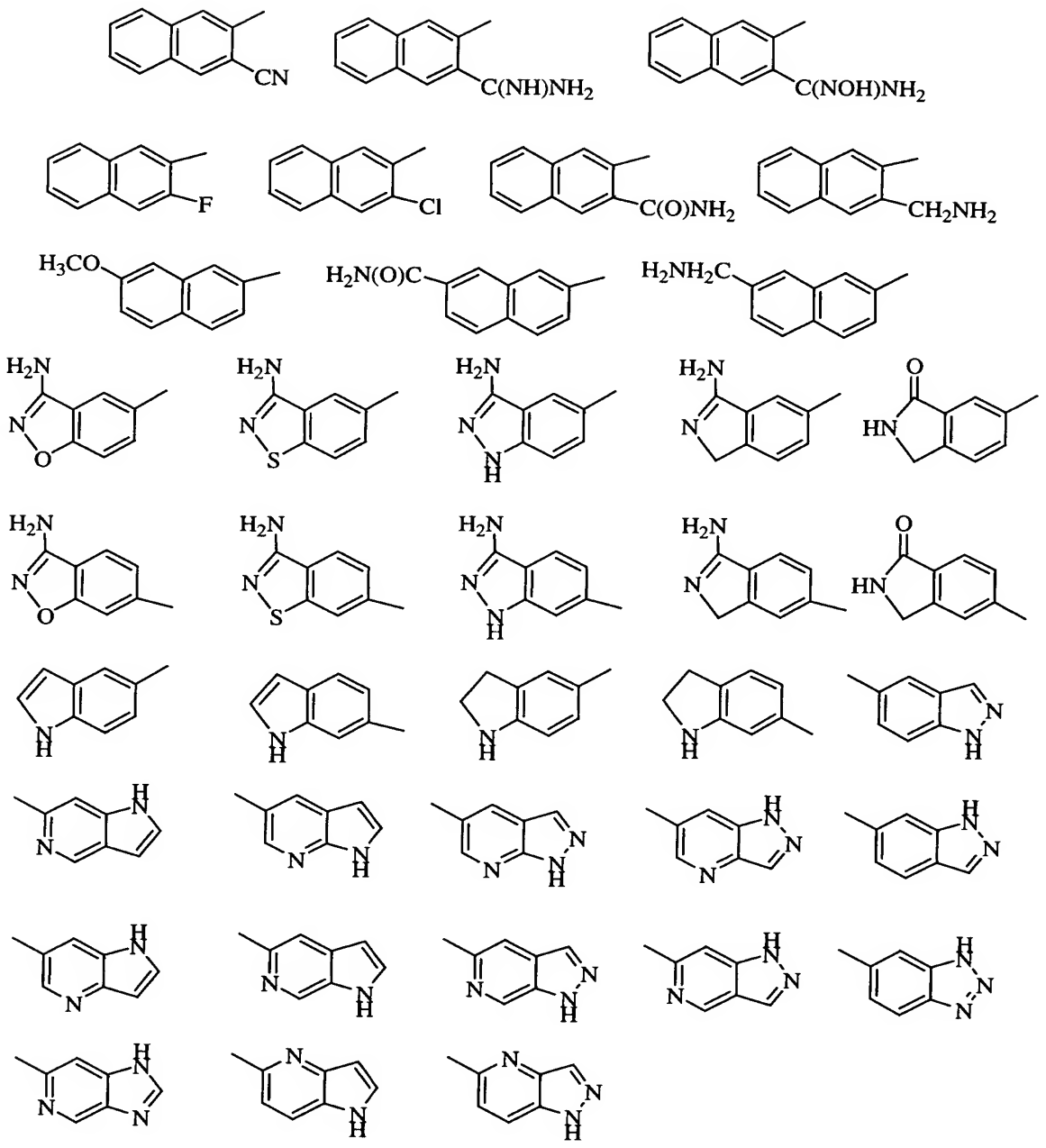
G is selected from the group:

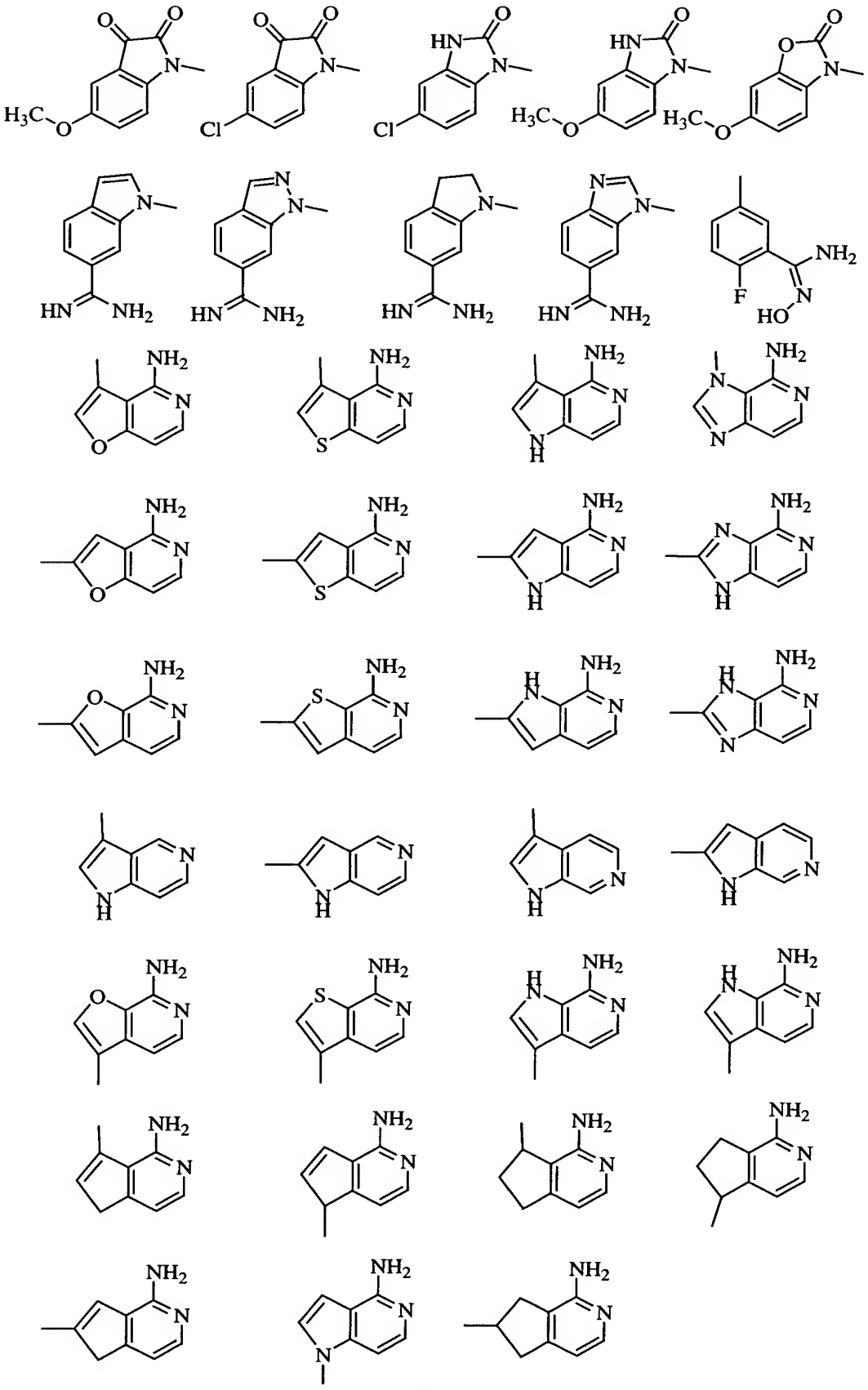


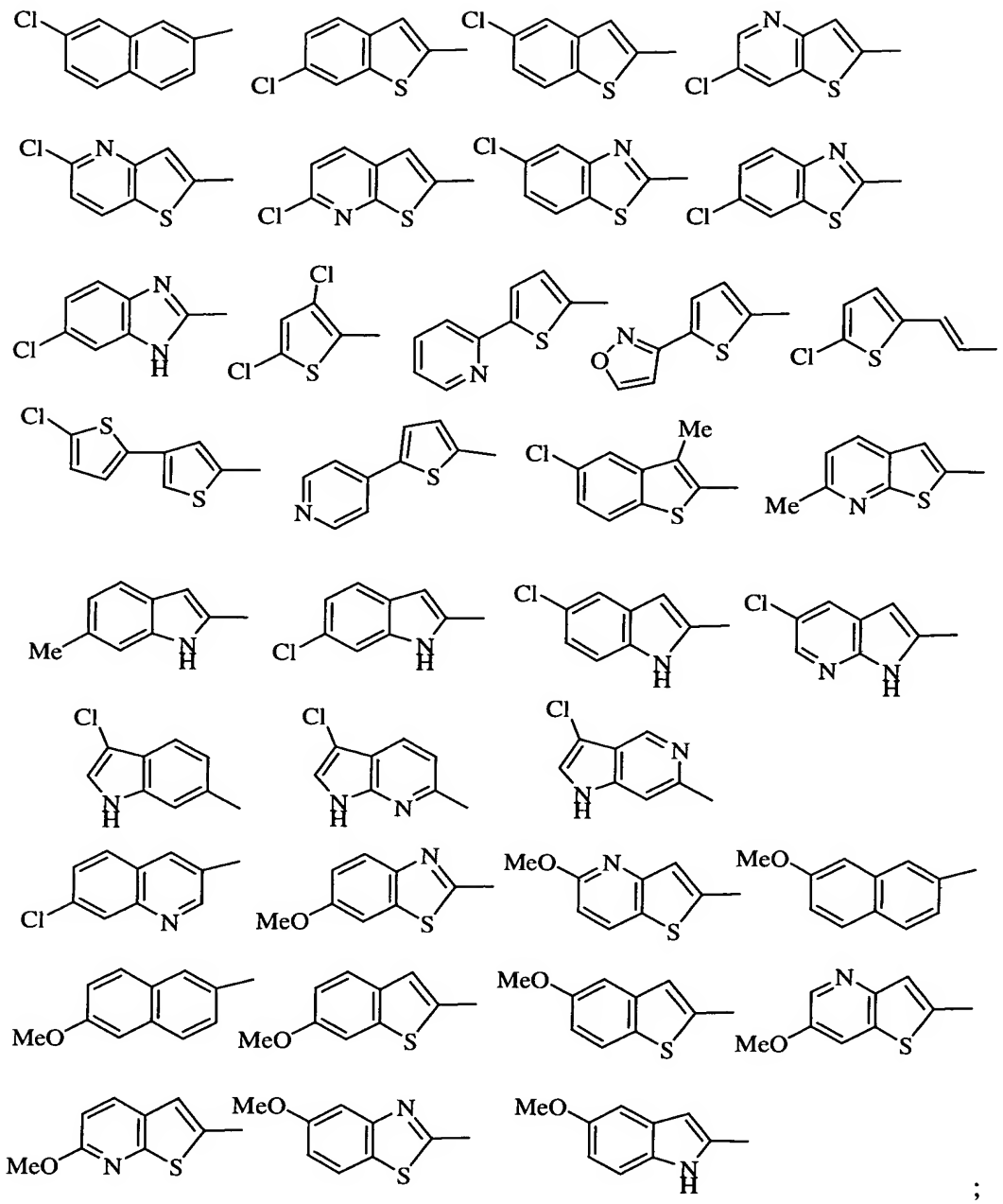










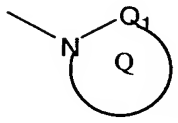


;

A is selected from one of the following carbocyclic and heterocyclic groups which are substituted with 0-2 R^4;

cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thienyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl,

1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolinyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

B is 

; provided that Z and B are attached to different atoms on A;

Q_1 is selected from C=O and SO_2;

ring Q is a 5-7 membered ring consisting of, in addition to the amide group shown, carbon atoms and 0-2 heteroatoms selected from NR^{4c}, O, S, S(O), and $S(O)_2$, wherein:

0-2 double bonds are present within the ring and the ring is substituted with 0-2 R^{4a};

alternatively, ring Q is a 5-7 membered ring to which another ring is fused, wherein:

the 5-7 membered ring consists of, in addition to the shown amide group, carbon atoms and 0-2 heteroatoms selected from NR^{4c}, O, S, S(O), and $S(O)_2$ and 0-1 double bonds are present within the ring;

the fusion ring is phenyl or a 5-6 membered heteroaromatic consisting of carbon atoms and 1-2 heteroatoms selected from NR^{4c}, O, and S;

ring Q, which includes the 5-7 membered ring and the fusion ring, is substituted with 0-3 R^{4a};

R^{1a}, at each occurrence, is selected from H, $-(CH_2)_r-R^{1b}$, $-(CH_2)_r-O-(CH_2)_r-R^{1b}$, $-(CH_2)_r-C(=NR^{1b})NR^3R^{1b}$, $NR^3(CR^3R^{3a})_tR^{1c}$, $O(CR^3R^{3a})_tR^{1c}$, $(CH_2)_rNR^3(CH_2)_rR^{1b}$, $(CH_2)_rC(O)NR^2(CH_2)_rR^{1b}$, $CO_2(CH_2)_tR^{1b}$, $O(CH_2)_tR^{1b}$, $S(O)_p(CH_2)_rR^{1d}$, $O(CH_2)_rR^{1d}$, $NR^3(CH_2)_rR^{1d}$, $OC(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)O(CH_2)_rR^{1d}$, and

$NR^3C(O)(CH_2)_rR^{1d}$, provided that R^{1a} forms other than an N-halo, N-S, O-O, or N-CN bond;

alternatively, when two R^{1a} groups are attached to the same carbon atom, together with the carbon atom to which they are attached they form a 3-6 membered carbocyclic or heterocyclic ring consisting of: carbon atoms and 0-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^4 and 0-3 ring double bonds;

R^{1b} is selected from H, CH_3, CH_2CH_3, F, Cl, Br, -CN, -CHO, CF_3, $(CH_2)_rOR^2$, NR^2R^{2a}, $C(O)R^{2b}$, CO_2R^{2b}, $OC(O)R^2$, CO_2R^{2a}, $S(O)_pR^2$, $NR^2(CH_2)_rOR^2$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2R^2$, $C(O)NR^2SO_2R^2$, $SO_2NR^2C(O)R^2$, C_{3-10} carbocycle substituted with 0-2 R^4, and 4-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^4, provided that R^{1b} forms other than an O-O, N-halo, N-S, or N-CN bond;

R^2, at each occurrence, is selected from H, CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, phenyl substituted with 0-2 R^{4b}, a benzyl substituted with 0-2 R^{4b}, and 5-6 membered aromatic heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-2 R^{4b}, and 5-6 membered aromatic heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-2 R^{4b}, and 5-6 membered aromatic heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-2 R^{4b}, and 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b};

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, -CN, NO_2, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $CH_2NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $CH_2C(O)NR^2R^{2a}$, $(CH_2)_rNR^3(CH_2)_{1-2}C(O)OR^3$, $(CH_2)_rNR^3(CH_2)_{2-4}NR^3R^{3a}$, $(CH_2)_rNR^3(CH_2)_{2-4}NR^3C(O)R^{3a}$, $(CH_2)_rNR^3(CH_2)_{2-4}NR^3SO_2R^{3a}$, $SO_2NR^2R^{2a}$, $CH_2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $CH_2NR^2SO_2$-C_{1-4} alkyl, $NR^2SO_2R^5$, $CH_2NR^2SO_2R^5$, $S(O)_pR^{5a}$, $CH_2S(O)_pR^{5a}$, CF_3, $(CH_2)_r$-3-7 membered carbocycle substituted with 0-1 R^5, and a $(CH_2)_r$-5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, CH_2OR^2, OR^2, F, Br, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$,

$CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, -CN, NO_2, $CH_2NR^2R^{2a}$, NR^2R^{2a}, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and $-CF_3$;

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, -CN, NO_2, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, $CH_2C(O)R^3$, $C(O)OR^{3c}$, $CH_2C(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $CH_2NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $CH_2C(O)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $CH_2SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $CH_2NR^3SO_2$-C_{1-4} alkyl, NR^3SO_2-phenyl, $CH_2NR^3SO_2$-phenyl, $S(O)_pCF_3$, $CH_2S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $CH_2S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, $CH_2S(O)_p$-phenyl, and CF_3;

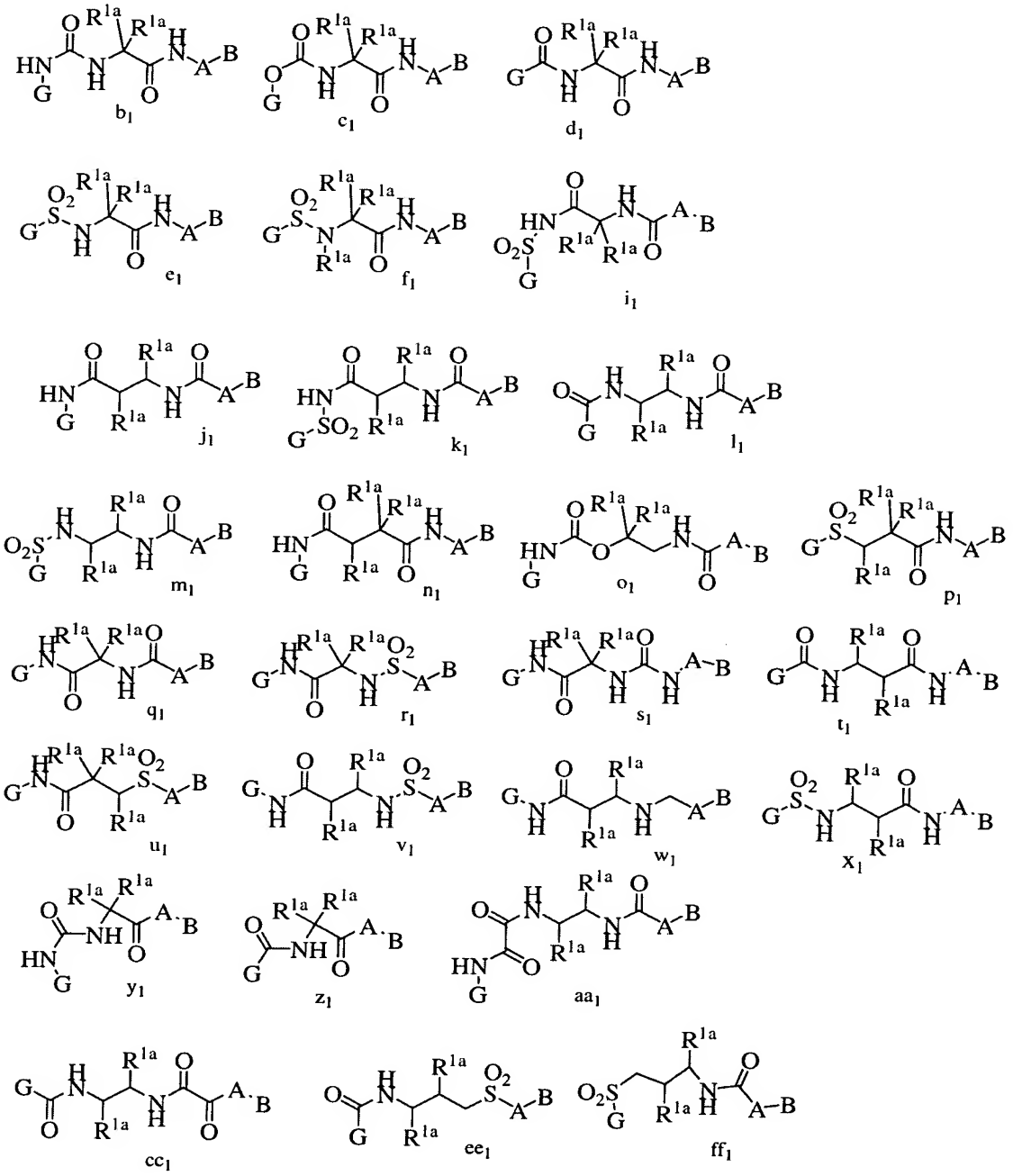
R^{4c}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, CH_2OR^2, CH_2F, CH_2Br, CH_2Cl, CH_2CN, CH_2NO_2, $CH_2NR^2R^{2a}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $CH_2NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $CH_2C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $CH_2SO_2NR^2R^{2a}$, $S(O)_pR^{5a}$, $CH_2S(O)_pR^{5a}$, CF_3, phenyl substituted with 0-1 R^5, and benzyl substituted with 0-1 R^5;

R^5, at each occurrence, is selected from H, =O, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, OR^3, CH_2OR^3, F, Cl, -CN, NO_2, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, $CH_2C(O)R^3$, $C(O)OR^{3c}$, $CH_2C(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, CF_3, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^6, at each occurrence, is selected from H, OH, OR^2, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, -CN, NO_2, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2b}$, $CH_2C(O)R^{2b}$, $NR^2C(O)R^{2b}$, $SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl; and

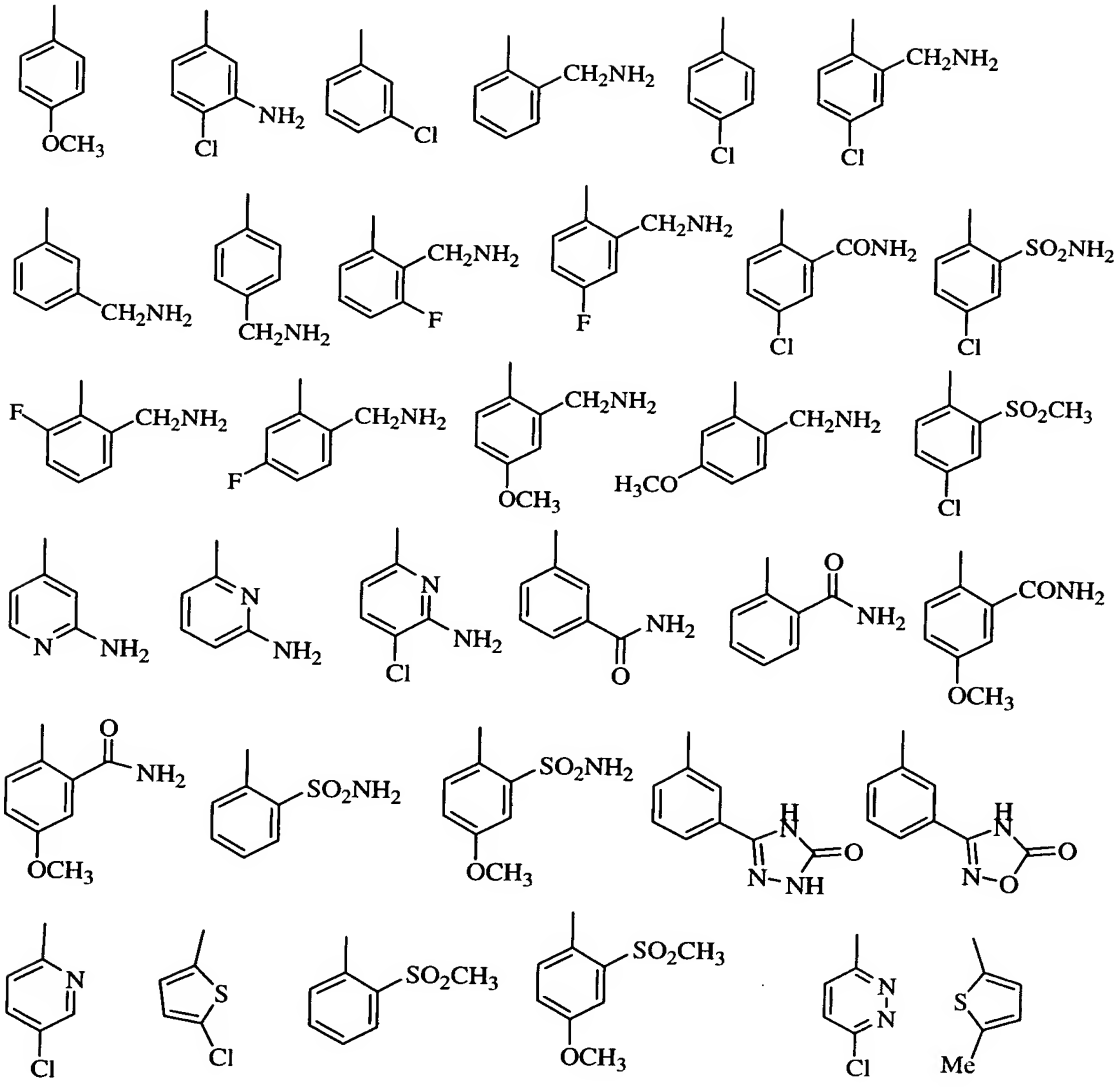
r, at each occurrence, is selected from 0, 1, and 2.

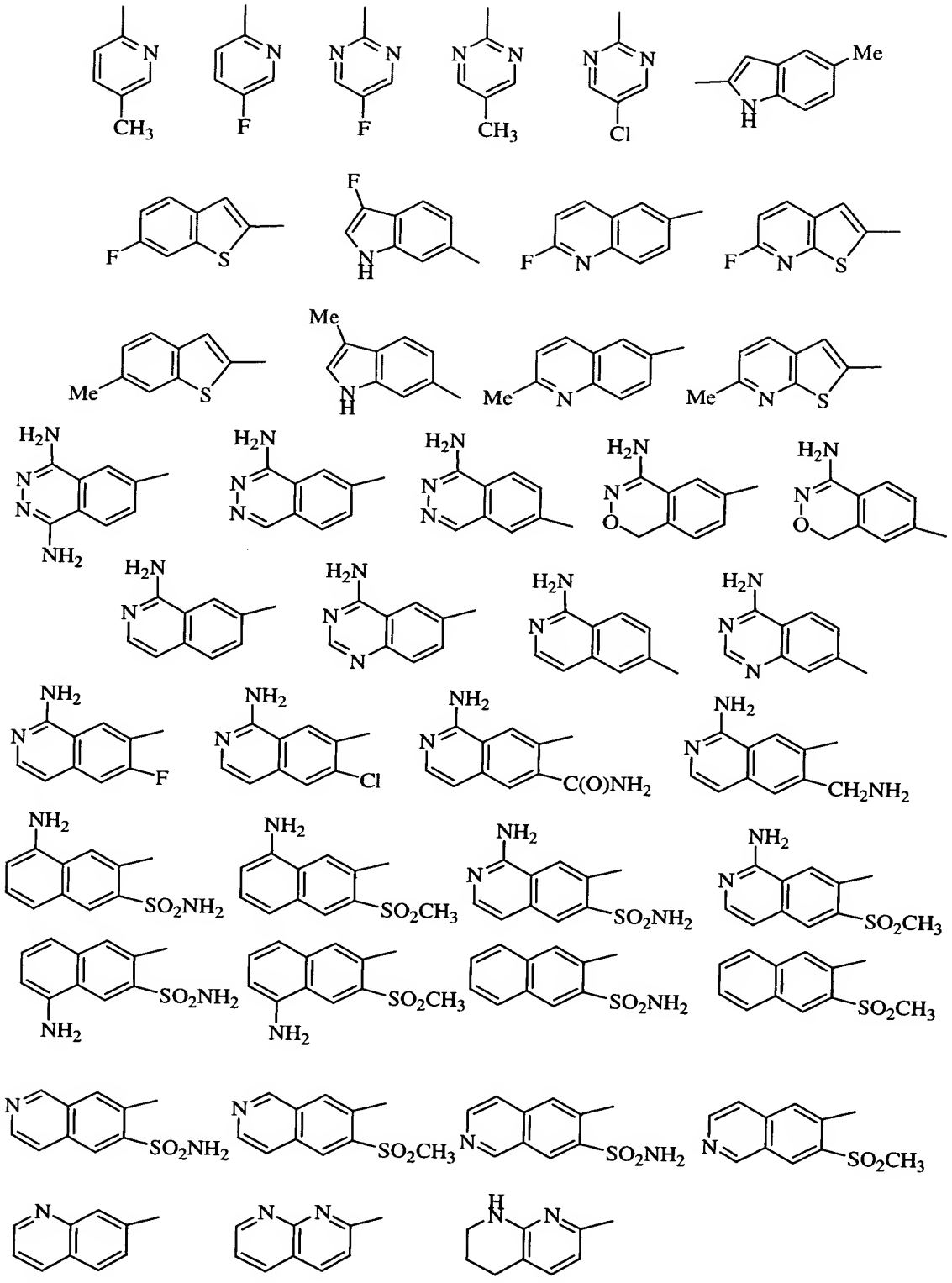
[4] In another preferred embodiment, the present invention provides a novel compound selected from b_1-f_1, i_1-aa_1, cc_1, ee_1, and ff_1:

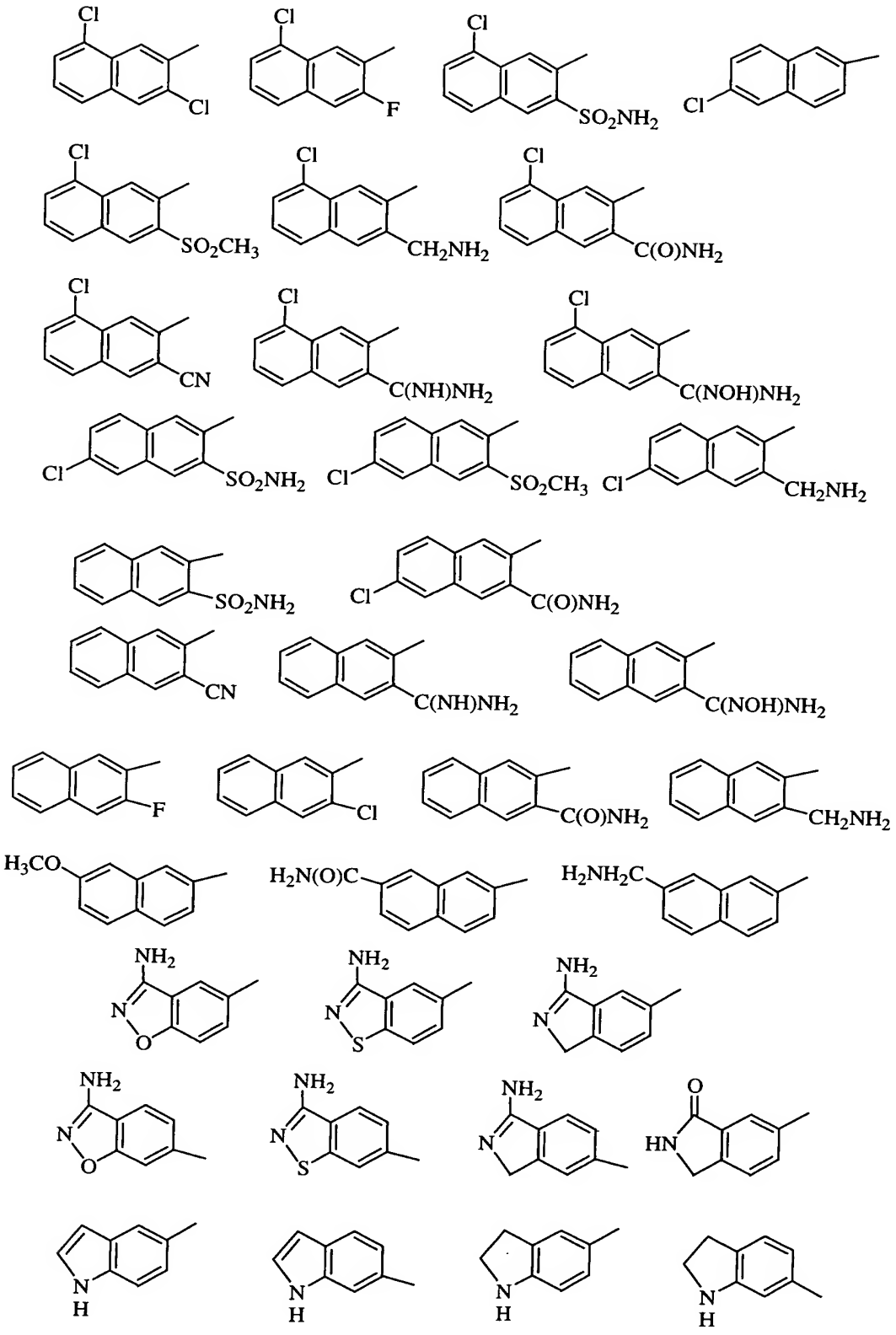


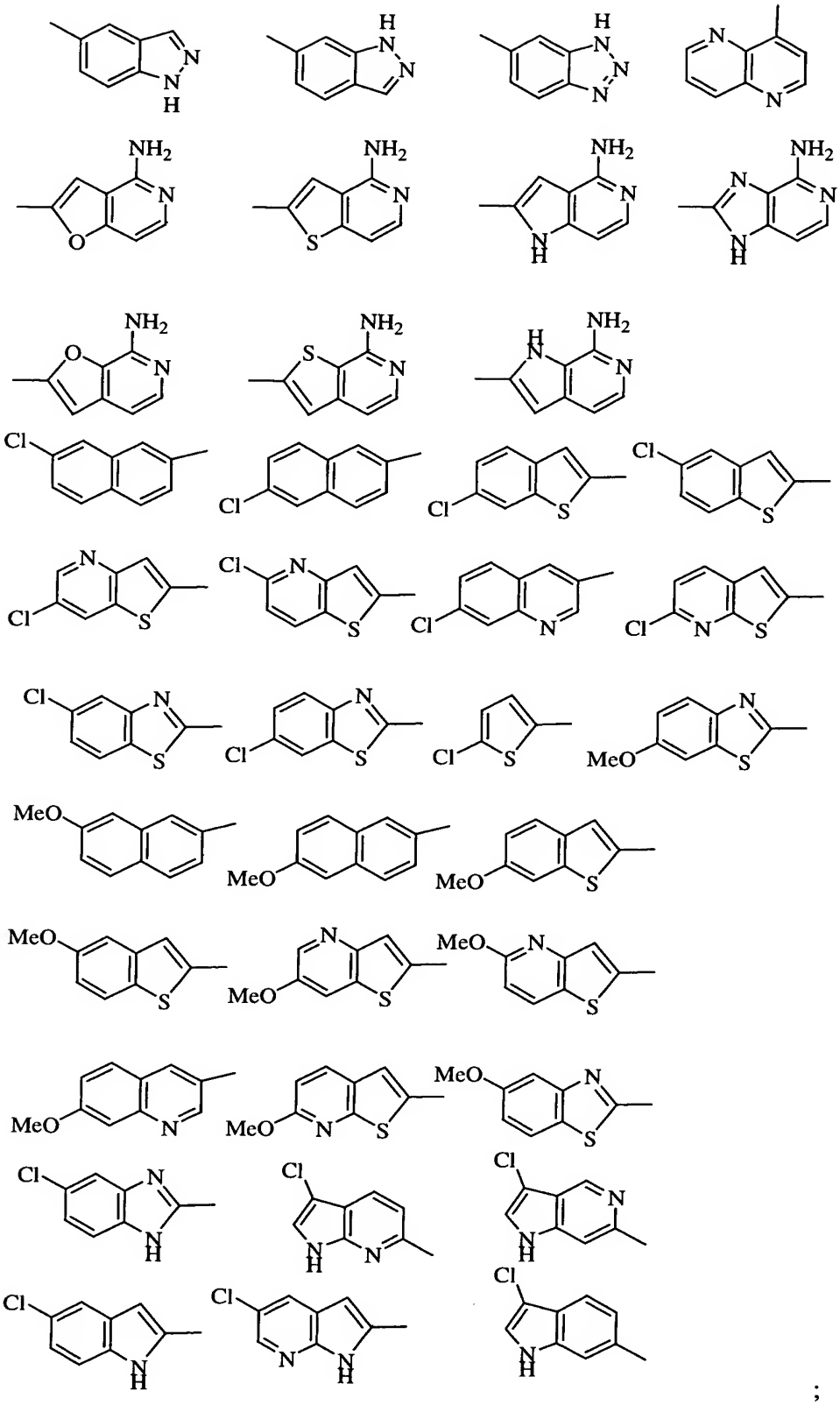
wherein:

G is selected from the group:



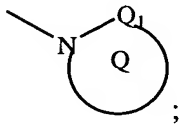






;

A is selected from cyclohexyl, piperidinyl, indolinyl, phenyl, pyridyl, thienyl, and pyrimidyl, and is substituted with 0-2 R^4;

B is  ; provided that Z and B are attached to different atoms on A;

Q_1 is selected from C=O and SO_2;

ring Q is a 5-6 membered ring consisting of, in addition to the amide group shown, carbon atoms and 0-1 heteroatoms selected from NR^{4c}, O, S, S(O), and $S(O)_2$, wherein:

0-2 double bonds are present within the ring and the ring is substituted with 0-2 R^{4a};

alternatively, ring Q is a 5-7 membered ring to which another ring is fused, wherein:

the 5-7 membered ring consists of, in addition to the shown amide group, carbon atoms and 0-1 heteroatoms selected from NR^{4c}, O, S, S(O), and $S(O)_2$ and 0-1 double bonds are present within the ring;

the fusion ring is phenyl;

ring Q, which includes the 5-7 membered ring and the fusion ring, is substituted with 0-2R^{4a};

R^{1a} is selected from H, R^{1b}, $C(CH_3)_2R^{1b}$, $CH(CH_3)R^{1b}$, CH_2R^{1b}, $CH_2CH_2R^{1b}$, $CH_2OCH_2CH_2R^{1b}$, $OCH_2CH_2R^{1b}$, $(CH_2)_rNR^3CH_2CH_2R^{1b}$, $NR^3(CR^3R^{3a})_tR^{1c}$, $O(CR^3R^{3a})_tR^{1c}$, $(CH_2)_rC(O)NR^2(CH_2)_rR^{1b}$, $S(O)_p(CH_2)_rR^{1d}$, $O(CH_2)_rR^{1d}$, $NR^3(CH_2)_rR^{1d}$, $OC(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)O(CH_2)_rR^{1d}$, and $NR^3C(O)(CH_2)_rR^{1d}$, provided that R^{1a} forms other than an N-halo, N-S, O-O, or N-CN bond;

alternatively, when two R^{1a} groups are attached to the same carbon atom, together with the carbon atom to which they are attached they form a 3-10 membered carbocyclic or heterocyclic ring consisting of: carbon atoms and 0-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^4 and 0-2 ring double bonds;

R^{1b} is selected from H, CH_3, CH_2CH_3, F, Cl, Br, -CN, -CHO, CF_3, $(CH_2)_rOR^2$, NR^2R^{2a}, $C(O)R^{2b}$, CO_2R^{2b}, $OC(O)R^2$, CO_2R^{2a}, $S(O)_pR^2$, $NR^2(CH_2)_rOR^2$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2R^2$, $C(O)NR^2SO_2R^2$, $SO_2NR^2C(O)R^2$, C_{3-6} carbocycle substituted with 0-2 R^4, and 4-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^4, provided that R^{1b} forms other than an O-O, N-halo, N-S, or N-CN bond;

R^2, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, phenyl substituted with 0-1 R^{4b}, benzyl substituted with 0-1 R^{4b}, and 5-6 membered aromatic heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^{4b};

R^{2a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-1 R^{4b}, and 5-6 membered aromatic heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-1 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2b}, at each occurrence, is selected from OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-1 R^{4b}, and 5-6 membered aromatic heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^{4b};

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-1 R^{4b}, and 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^{4b};

R^4, at each occurrence, is selected from H, =O, OR^2, CH_2OR^2, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, -CN, NO_2, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $CH_2C(O)NR^2R^{2a}$, $NR^3(CH_2)_{1-2}C(O)OR^3$, $NR^3(CH_2)_2NR^3R^{3a}$, $NR^3(CH_2)_2NR^3C(O)R^{3a}$, $NR^3(CH_2)_2NR^3SO_2R^{3a}$, $SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^{5a}$, CF_3, $(CH_2)_r$-3-7 membered carbocycle substituted with 0-1 R^5, and a $(CH_2)_r$-5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, CH_2OR^2, OR^2, F, Br, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, $CH_2NR^2R^{2a}$, NR^2R^{2a}, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3;

R^{4b}, at each occurrence, is selected from H, =O, OR^3, CH_2OR^3, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, -CN, NO_2, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$,

$C(O)OR^{3c}$, $CH_2C(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $CH_2C(O)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, NR^3SO_2-phenyl, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, and CF_3;

R^{4c}, at each occurrence, is selected from H, CH_3, CH_2CH_3, phenyl substituted with 0-1 R^5, and benzyl substituted with 0-1 R^5;

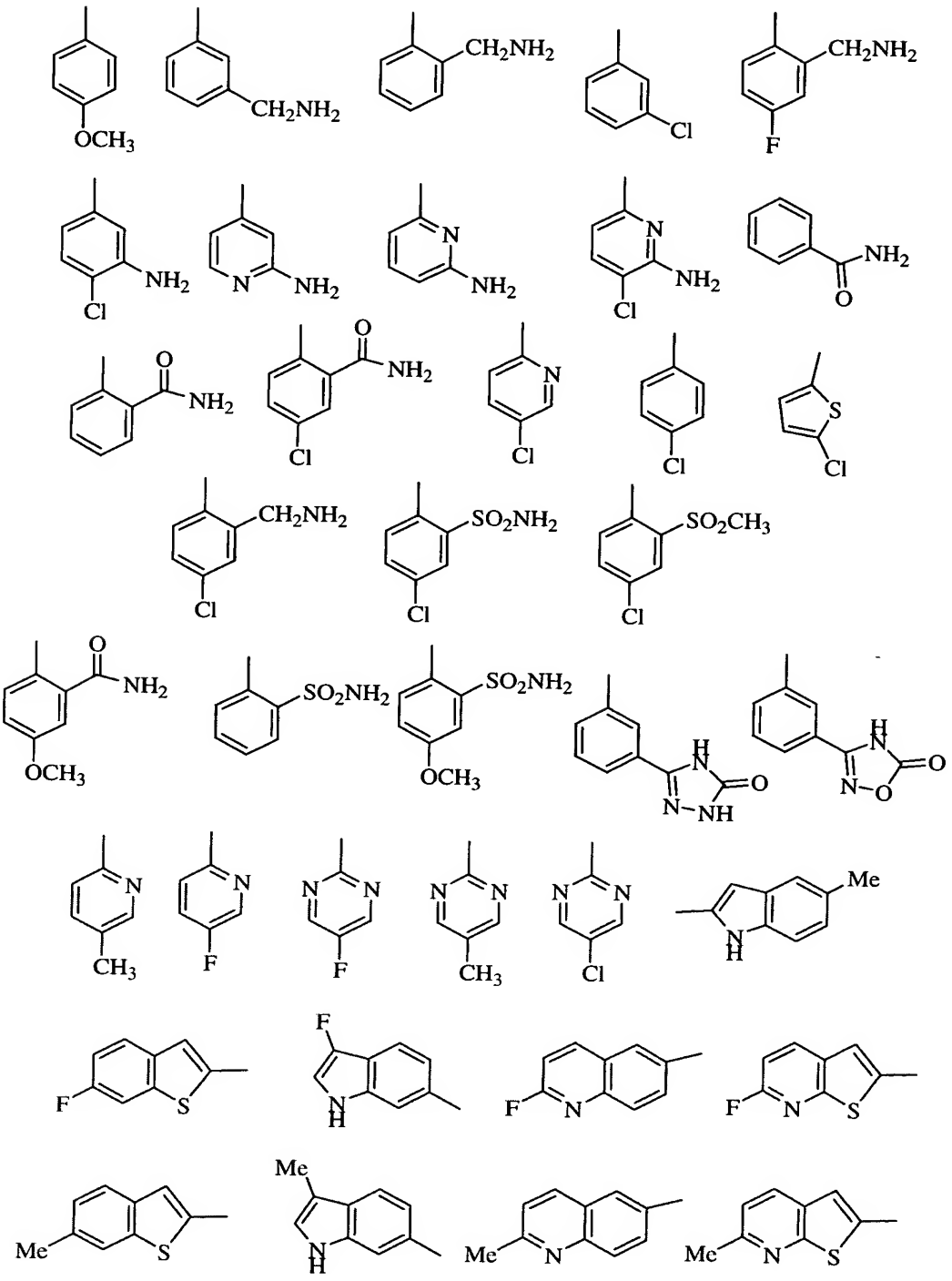
R^5, at each occurrence, is selected from H, =O, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, OR^3, CH_2OR^3, F, Cl, -CN, NO_2, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, $C(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, NR^3SO_2-phenyl, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, CF_3, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6; and

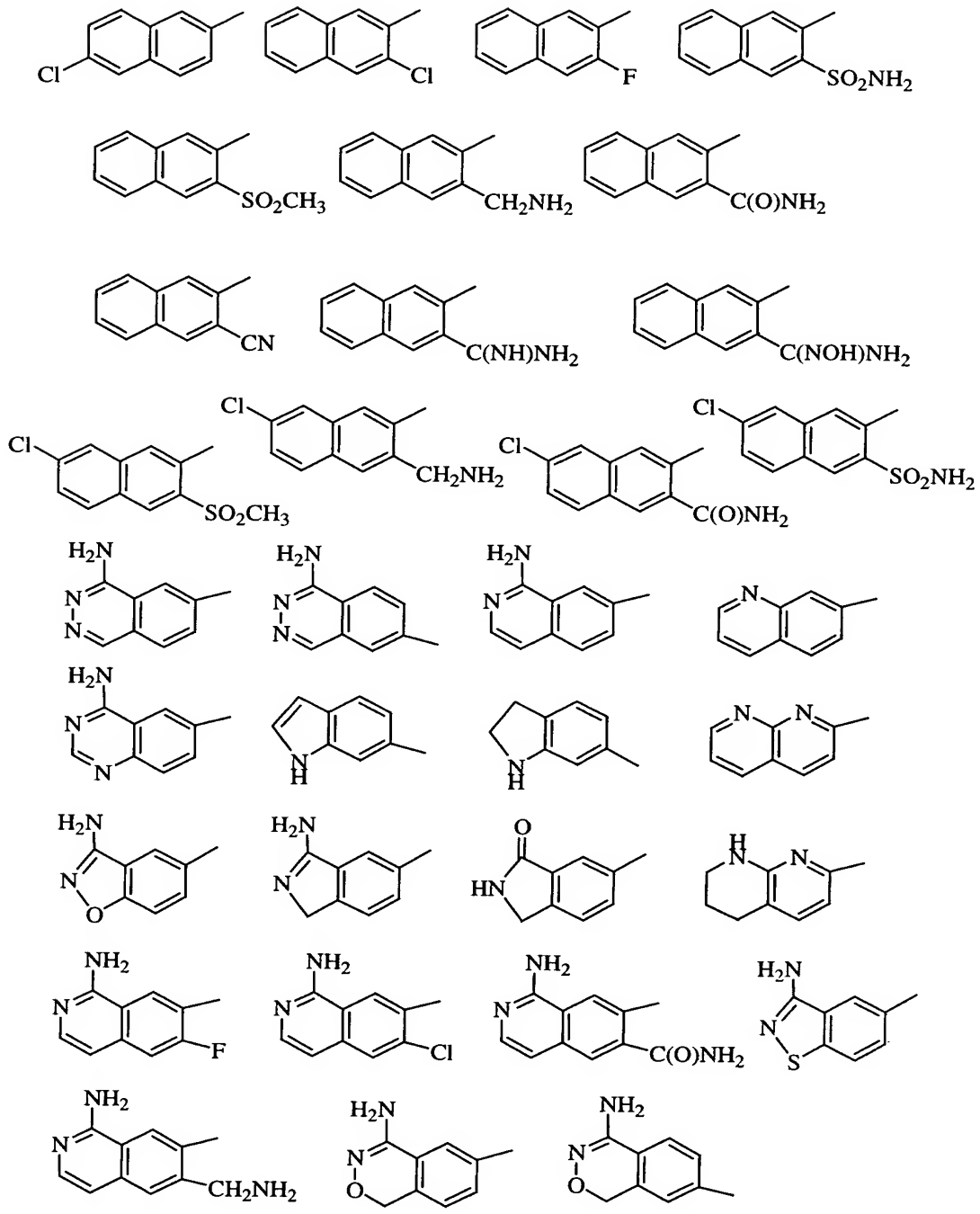
R^6, at each occurrence, is selected from H, OH, OR^2, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, -CN, NO_2, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2b}$, $CH_2C(O)R^{2b}$, $NR^2C(O)R^{2b}$, and $SO_2NR^2R^{2a}$.

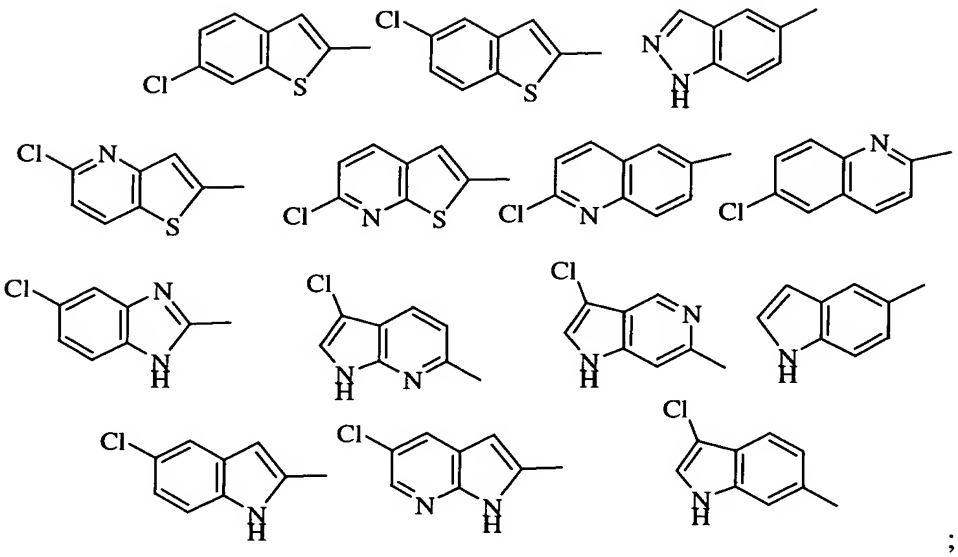
[5] In another preferred embodiment, the present invention provides a novel compound, wherein:

M is 4-7 membered linear chain consisting of: carbon atoms, 1-2 carbonyl groups, and 1-3 heteroatoms selected from O, $S(O)_p$, and N, and M is substituted with 0-3 R^{1a} and 0-1 R^2, provided that other than an S-S, S-O, or O-O bond is present in M;

G is selected from:



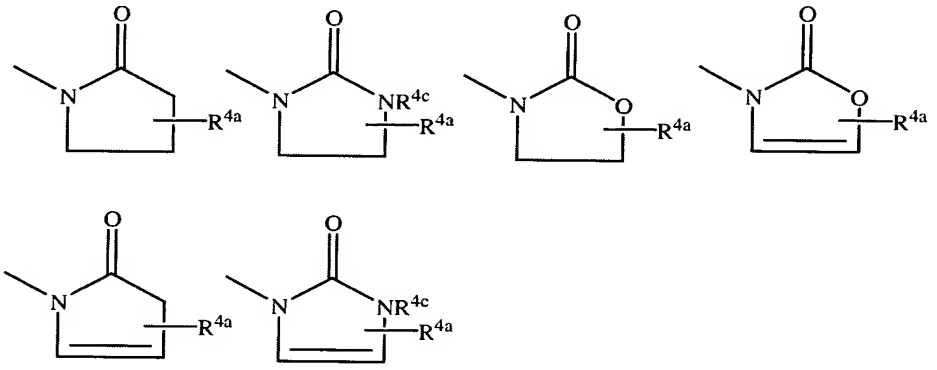


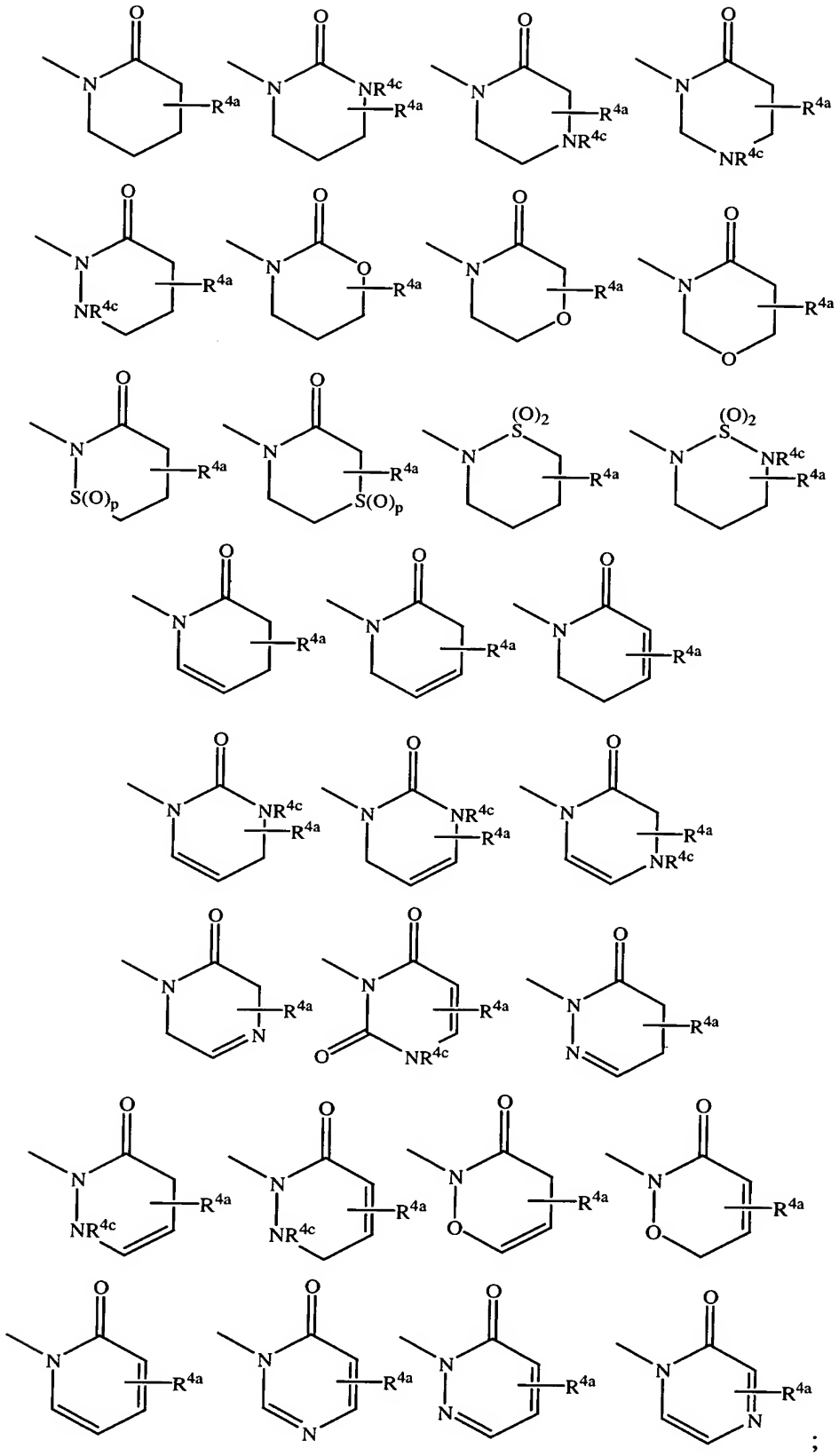


;

A is selected from the group: cyclohexyl, piperidinyl, indolinyl, phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl;

B is attached to a different atom on A than Z and is selected from the group:





;

R^{1a} is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2(CH_3)_2$, CF_3, CH_2CF_3, OCH_3, CH_2OH, $C(CH_3)_2OH$, CH_2OCH_3, NH_2, CH_2NH_2, $NHCH_3$, CH_2NHCH_3, $N(CH_3)_2$, $CH_2N(CH_3)_2$, CO_2H, $COCH_3$, CO_2CH_3, $CH_2CO_2CH_3$, $NHCOCH_3$, $S(O)CH_3$, $CH_2S(O)CH_3$, $S(O)_2CH_3$, $CH_2S(O)_2CH_3$, $C(O)NH_2$, $CH_2C(O)NH_2$, SO_2NH_2, $CH_2SO_2NH_2$, $NHSO_2CH_3$, $CH_2NHSO_2CH_3$, $NHSO_2NHCH_3$, $NHSO_2N(CH_3)_2$, $NHCO_2R^{2a}$, $NHC(O)NHR^{2a}$, $CH_2OCH_2CH_2NR^2R^{2a}$, $C(O)NR^2R^{2a}$, $CH_2CH_2OR^2$, $CH_2C(O)NR^2CH_2CH_2OR^2$, $C(O)NHCH_2CH_2NR^2R^{2a}$, $CH_2C(O)NHCH_2CH_2NR^2R^{2a}$, $C(O)NCH_3CH_2CH_2NR^2R^{2a}$, $CH_2C(O)NCH_3CH_2CH_2NR^2R^{2a}$, $CH_2NHCH_2CH_2NR^2R^{2a}$, $CH_2N(CH_3)CH_2CH_2NR^2R^{2a}$, phenyl substituted with 0-2 R^{4b}, -CH_2-phenyl substituted with 0-2 R^{4b}, 5-10 membered aromatic heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b}, and –CH_2-5-10 membered aromatic heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b}, provided that R^{1a} forms other than an N-halo, N-S, O-O, or N-CN bond;

R^2, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, phenyl substituted with 0-1 R^{4b}, benzyl substituted with 0-1 R^{4b}, and 5 membered aromatic heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^{4b};

R^{2a}, at each occurrence, is selected from H, CH_3, and CH_2CH_3;

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring

substituted with 0-1 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2b}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, and CH_2CH_3;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, and CH_2CH_3;

R^4, at each occurrence, is selected from H, =O, OR^2, CH_2OR^2, F, Cl, CH_3, CH_2CH_3, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $CH_2C(O)NR^2R^{2a}$, $NR^3CH_2C(O)OR^3$, $NR^3CH_2CH_2C(O)OR^3$, $NR^3(CH_2)_2NR^3R^{3a}$, $NR^3(CH_2)_2NR^3C(O)R^{3a}$, $NR^3(CH_2)_2NR^3SO_2R^{3a}$, $NR^2SO_2R^5$, $S(O)_2CH_3$, $S(O)_2$-phenyl, CF_3, $(CH_2)_r$-3-7 membered carbocycle substituted with 0-1 R^5, and a $(CH_2)_r$-5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, and $C(CH_3)_3$;

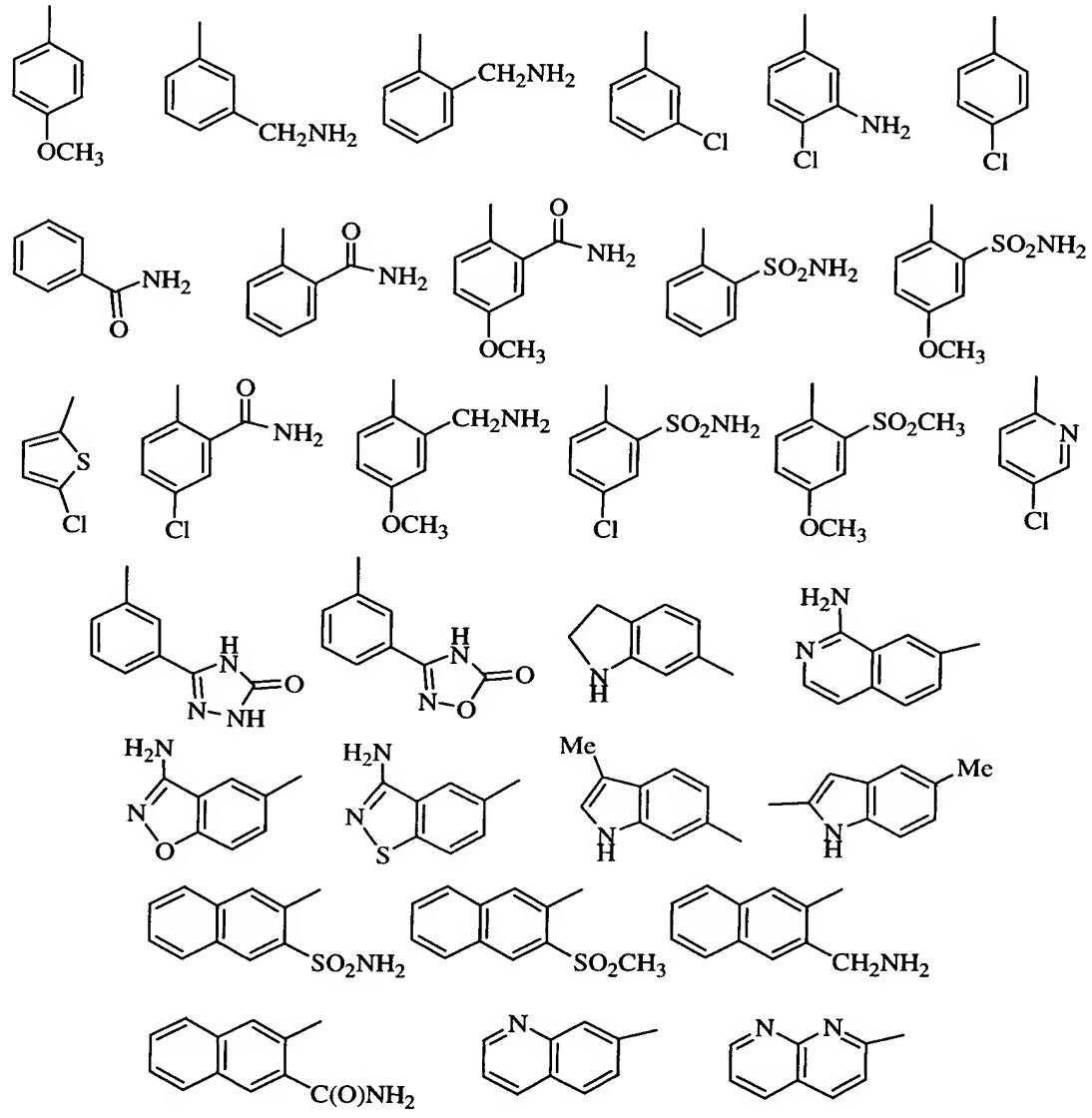
R^{4b}, at each occurrence, is selected from H, =O, OR^3, CH_2OR^3, F, Cl, CH_3, CH_2CH_3, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, $C(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $CH_2C(O)NR^3R^{3a}$, NR^3SO_2-phenyl, $S(O)_2CH_3$, $S(O)_2$-phenyl, and CF_3;

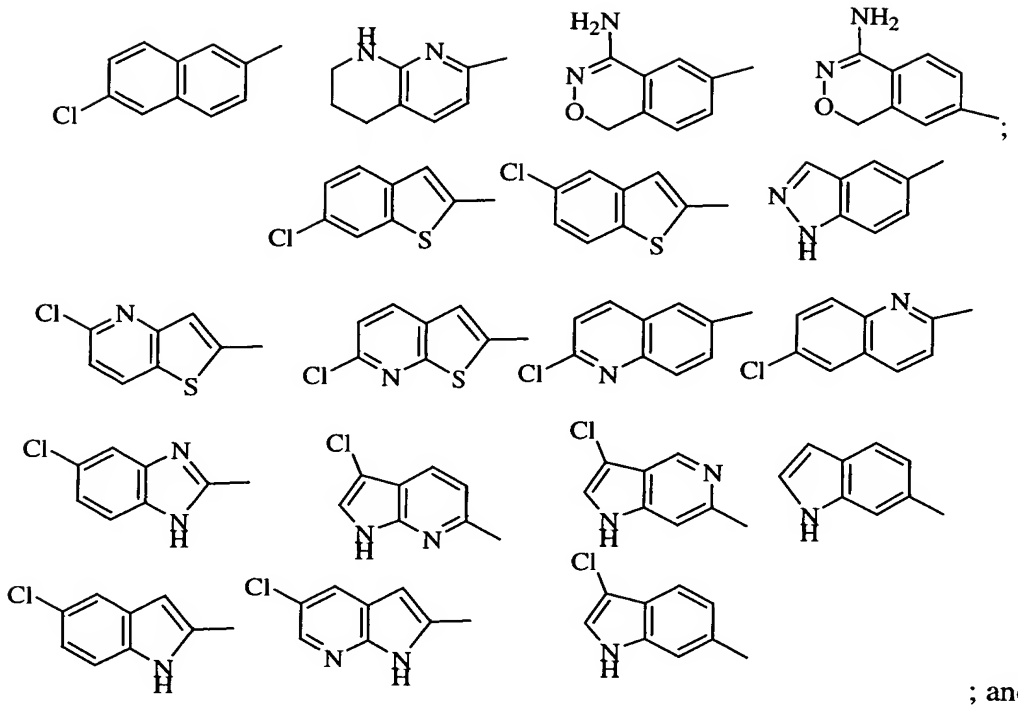
R^5, at each occurrence, is selected from H, =O, CH_3, CH_2CH_3, OR^3, CH_2OR^3, F, Cl, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, $C(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, NR^3SO_2-phenyl, $S(O)_2$-CH_3, $S(O)_2$-phenyl, CF_3, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6; and,

R^6, at each occurrence, is selected from H, OH, OR^2, F, Cl, CH_3, CH_2CH_3, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2b}$, $CH_2C(O)R^{2b}$, $NR^2C(O)R^{2b}$, and $SO_2NR^2R^{2a}$.

[6] In another preferred embodiment, the present invention provides a novel compound, wherein:

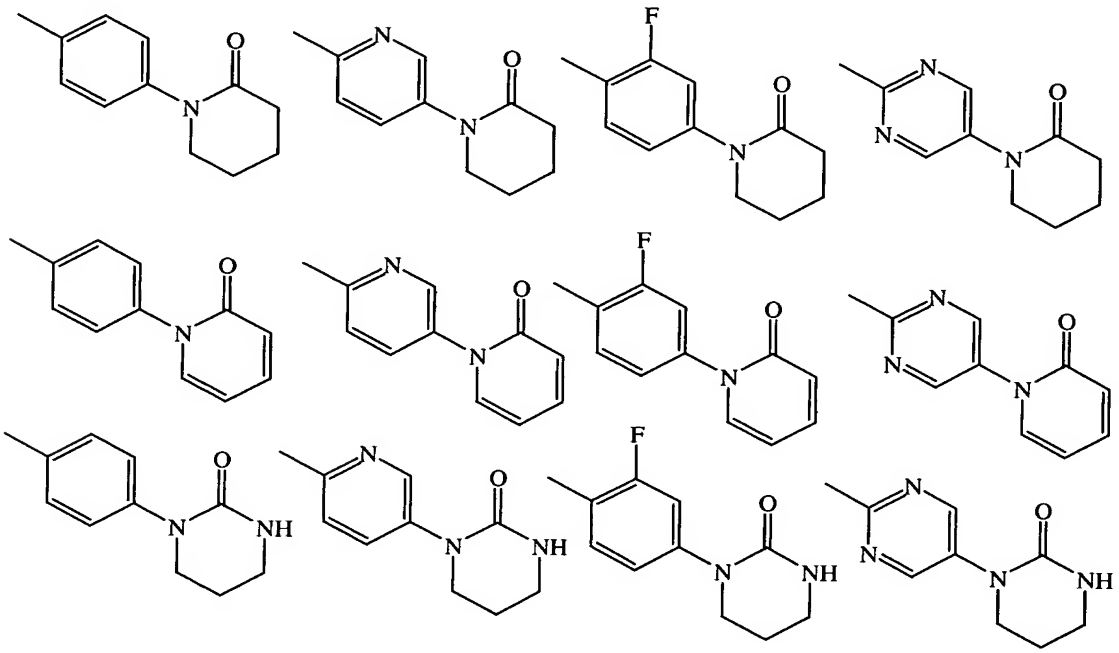
G is selected from:





; and,

A-B is selected from:



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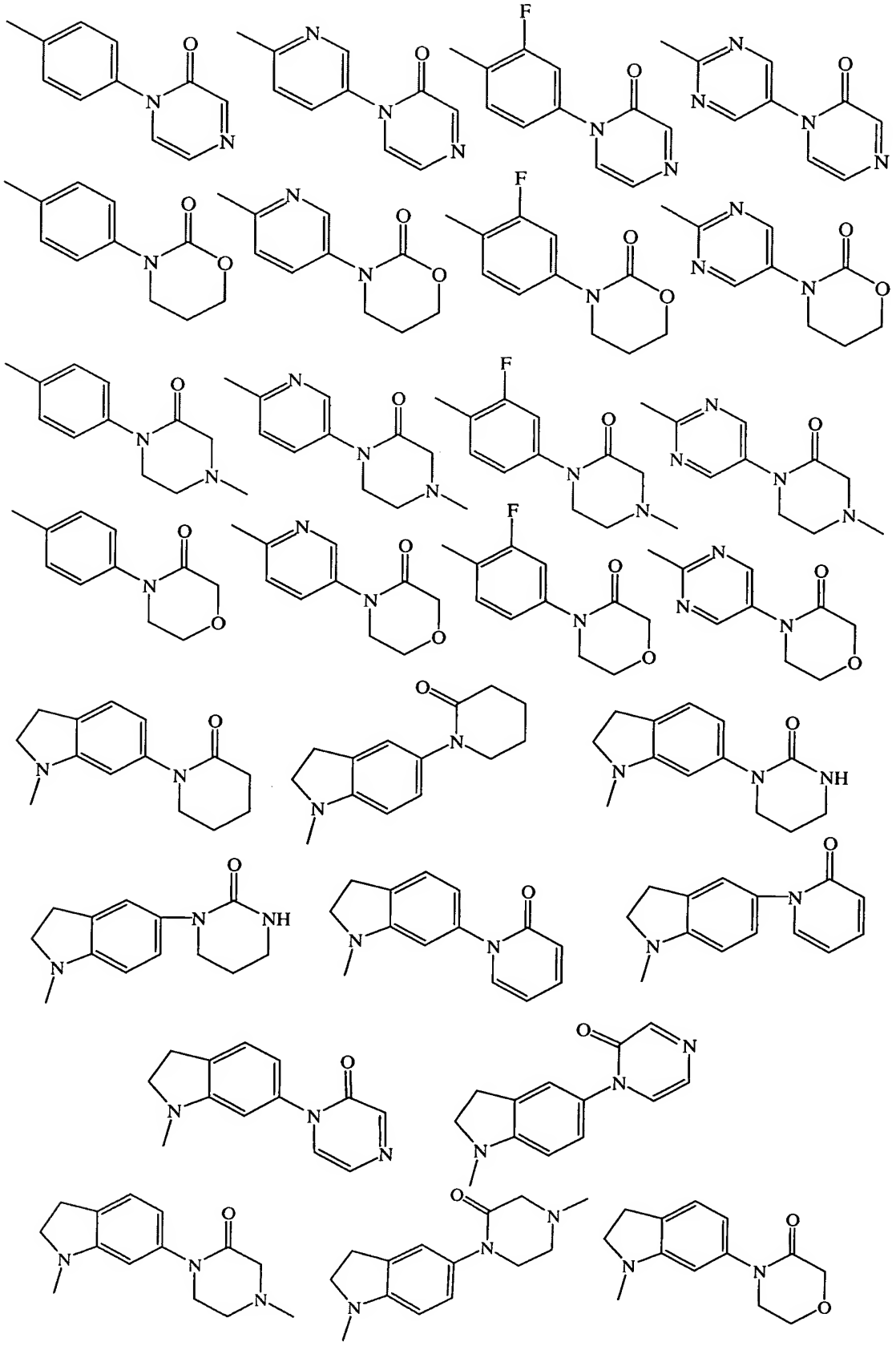
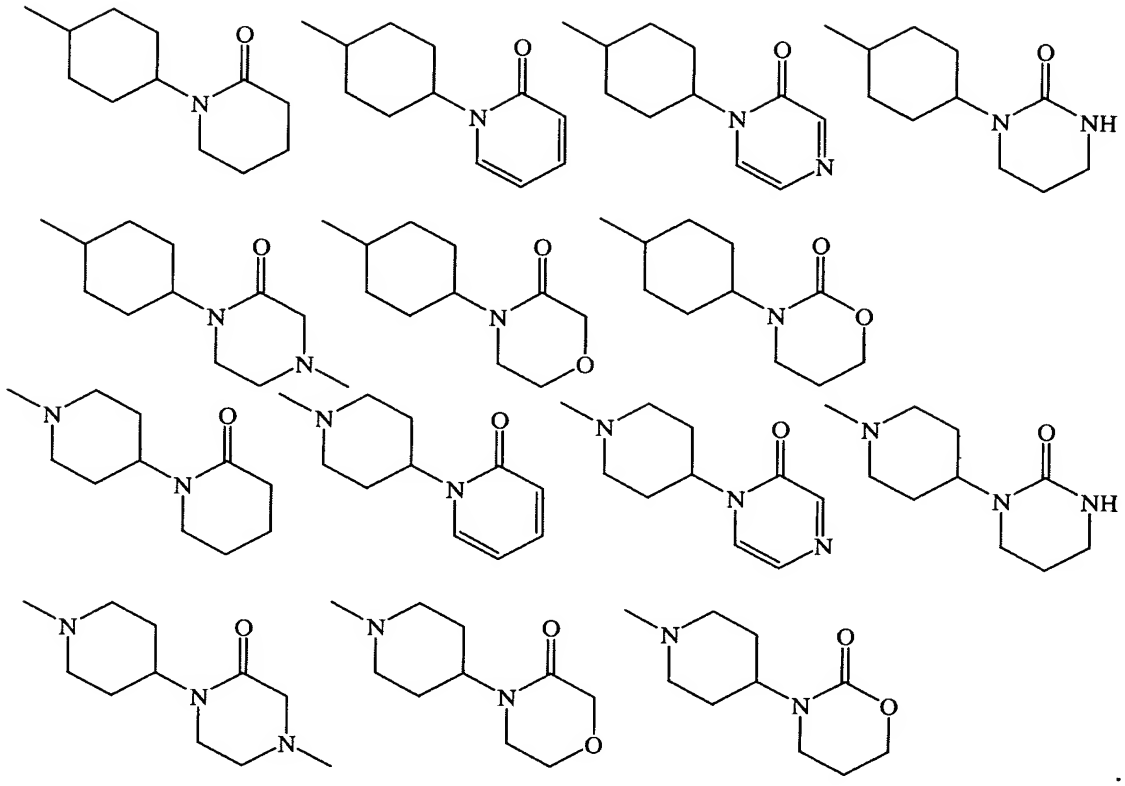
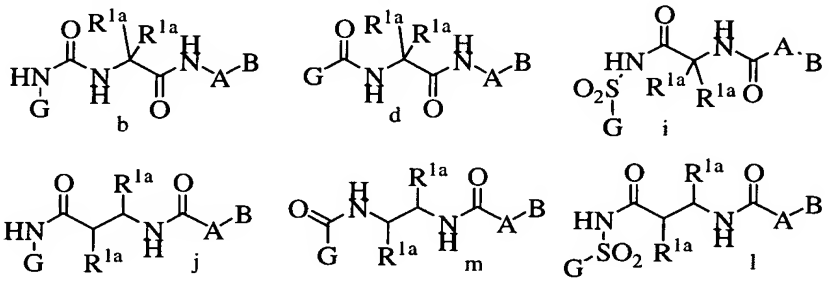


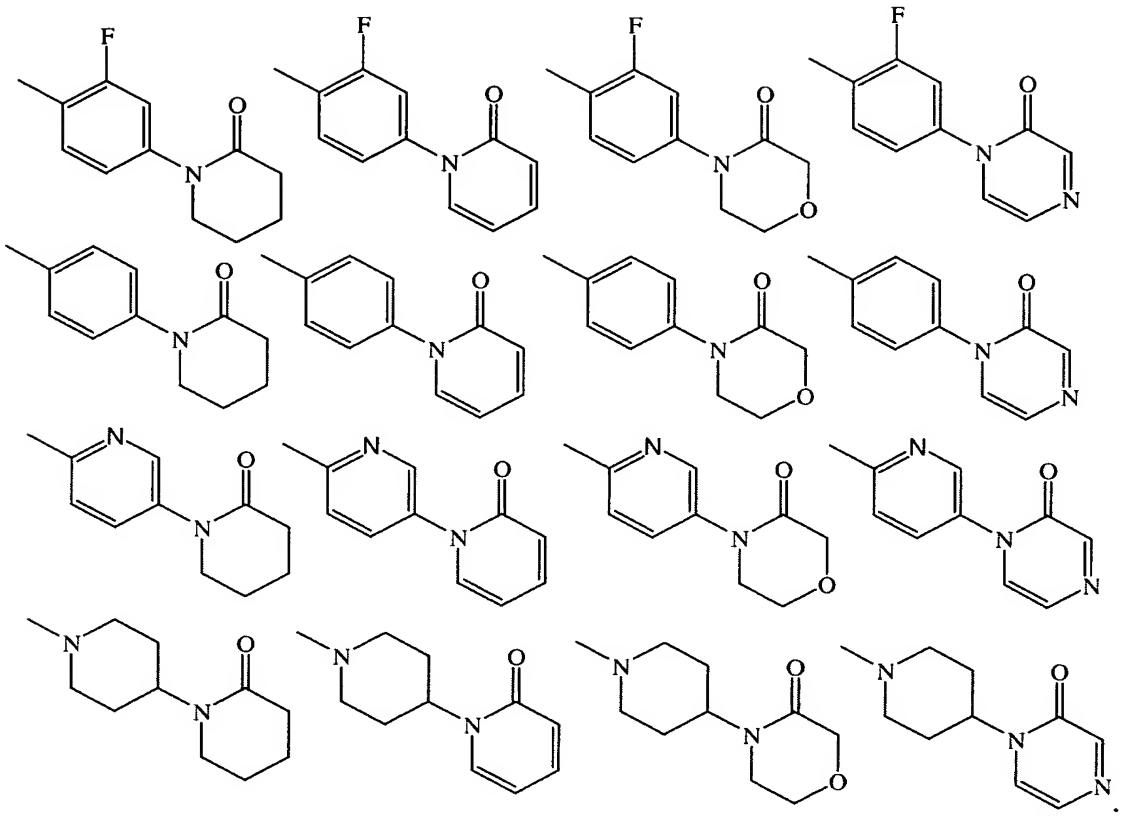


[7] In another preferred embodiment, the present invention provides a novel compound, wherein the compound is selected from:



and,

A-B is selected from:



[8] In another preferred embodiment, the present invention provides a novel compound, wherein the compound is selected from the group:

2-(5-Chloro-thiophene-2-sulfonylamino)-*N*-[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide;

2-(6-Chloro-naphthalene-2-sulfonylamino)-*N*-[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide;

5-Chloro-thiophene-2-carboxylic acid {[4-(2-oxo-2*H*-pyridin-1-yl)-phenylcarbamoyl]-phenyl-methyl}-amide;

5-Chloro-1*H*-indole-2-carboxylic acid {[4-(2-oxo-2*H*-pyridin-1-yl)-phenylcarbamoyl]-phenyl-methyl}-amide;

3-Chloro-1*H*-indole-6-carboxylic acid {[4-(2-oxo-2*H*-pyridin-1-yl)-phenylcarbamoyl]-phenyl-methyl}-amide;

1*H*-Indole-6-carboxylic acid {[4-(2-oxo-2*H*-pyridin-1-yl)-phenylcarbamoyl]-phenyl-methyl}-amide;

2-*R*-(6-Chloro-naphthalene-2-sulfonylamino)-*N*-[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide;

2-*S*-(6-Chloro-naphthalene-2-sulfonylamino)-*N*-[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide;

2-(5-Chloro-thiophene-2-sulfonylamino)-*N*-[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide;

N-β-(6-chloro-naphthalene-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide;

N-[β-(4-methoxyl-benzenesulfonylamino)-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)benzamide;

N-[2-(5-Chloro-pyridin-2-ylcarbamoyl)ethyl]-4-(2-oxo-2*H*-pyridin-1-yl)benzamide;

3-Chloro-1*H*-indole-6-carboxylic acid {2-[4-(2-oxo-2*H*-pyridin-1-yl)benzoylamino]ethyl}amide;

5-Chloro-thiophene-2-carboxylic acid {2-[4-(2-oxo-2*H*-pyridin-1-yl)benzoylamino]ethyl}amide;

5-Chloro-1*H*-indole-2-carboxylic acid {2-[4-(2-oxo-2*H*-pyridin-1-yl)benzoylamino]ethyl}amide;

N-{4-[(4-Chloro-phenylcarbamoyl)-methyl]-tetrahydro-pyran-4-yl}-4-(2-oxo-2H-pyridin-1-yl)-benzamide; and

2-[(5-Chloro-thiophene-2-carbonyl)-amino]-3-[4-(2-oxo-2H-pyridin-1-yl)-benzoylamino]-propionic acid methyl ester;

or a pharmaceutically acceptable salt form thereof.

[9] In another preferred embodiment, the present invention provides a novel compound, wherein the compound is selected from Examples 19-454 of Table 1.

In another embodiment, the present invention provides a novel pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method for treating a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another preferred embodiment, the present invention provides a novel method, wherein the thromboembolic disorder is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart.

In another preferred embodiment, the present invention provides a novel method, wherein the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial

thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, or (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis.

In another embodiment, the present invention provides a novel method of treating a patient in need of thromboembolic disorder treatment, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a thromboembolic disorder

In another embodiment, the present invention provides a novel method, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a thromboembolic disorder.

In another embodiment, the present invention provides a novel method for treating a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a first and second therapeutic agent, wherein the first therapeutic agent is compound of the present invention or a pharmaceutically acceptable salt thereof and the second therapeutic agent is at least one agent selected from a second factor Xa inhibitor, an anti-coagulant agent, an anti-platelet agent, a thrombin inhibiting agent, a thrombolytic agent, and a fibrinolytic agent.

In another preferred embodiment, the present invention provides a novel method, wherein the second therapeutic agent is at least one agent selected from warfarin, unfractionated heparin, low molecular weight heparin, synthetic pentasaccharide, hirudin, argatrobanas, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, melagatran, disulfatohirudin, tissue plasminogen activator, modified tissue plasminogen activator, anistreplase, urokinase, and streptokinase.

In another preferred embodiment, the present invention provides a novel method, wherein the second therapeutic agent is at least one anti-platelet agent.

In another preferred embodiment, the present invention provides a novel method, wherein the anti-platelet agent is aspirin and clopidogrel.

In another preferred embodiment, the present invention provides a novel method, wherein the anti-platelet agent is clopidogrel.

In another embodiment, the present invention provides a novel article of manufacture, comprising:

(a) a first container;

(b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and,

(c) a package insert stating that the pharmaceutical composition can be used for the treatment of a thromboembolic disorder.

In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising:

(d) a second container;

wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

In another embodiment, the present invention provides a novel article of manufacture, comprising:

(a) a first container;

(b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and,

(c) a package insert stating that the pharmaceutical composition can be used in combination with a second therapeutic agent to treat a thromboembolic disorder.

In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising:

(d) a second container;

wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

In another embodiment, the present invention provides novel compounds as described above for use in therapy.

In another embodiment, the present invention provides the use of novel compounds as described above for the manufacture of a medicament for the treatment of a thromboembolic disorder.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional more preferred embodiments. It is also to be understood that each individual element of the preferred embodiments is intended to be taken individually as its own independent preferred embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may

be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. All tautomers of shown or described compounds are also considered to be part of the present invention.

The term "linear chain," as used herein to describe linker M, is intended to mean a series of atoms (i.e., carbon, oxygen, nitrogen, and sulfur) that are connected together one at a time to form a chain. Thus, a chain atom is connected to one other chain atom if it is a terminal atom or two other chain atoms if is non-terminal. None of these chain atoms are bonded together, directly or indirectly, through a ring. Examples of a 5-membered linear chain include $C(O)NHCH_2NHC(O)$ and $NHC(O)CH_2S(O)_2NH$, but not 1-amino-2-carbamoyl-cyclohexane. The number of chain atoms is determined by counting each atom in the chain, but not any atom substituted thereon. Thus, the 3 oxygen atoms and 4 hydrogen atoms of the group $S(O)_2NHCH_2NHC(O)$ are not counted, and $S(O)_2NHCH_2NHC(O)$ is a 5-membered chain, not a 12-membered chain.

Preferably, the molecular weight of compounds of the present invention is less than about 500, 550, 600, 650, 700, 750, or 800 grams per mole. Preferably, the molecular weight is less than about 800 grams per mole. More preferably, the molecular weight is less than about 750 grams per mole. Even more preferably, the molecular weight is less than about 700 grams per mole.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N). The present invention, in general, does not cover groups such as N-halo, S(O)H, and SO_2H.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In cases wherein there are amines on the compounds of this invention, these can be converted to amine N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, all shown and claimed amines are considered to cover both the shown amine and its N-oxide (N→O) derivative.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. $C_{1\text{-}6}$ alkyl, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and

pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-6} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-7} cycloalkyl is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Alkenyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more unsaturated carbon-carbon bonds that may occur in any stable point along the chain, such as ethenyl and propenyl. C_{2-6} alkenyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. "Alkynyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more triple carbon-carbon bonds that may occur in any stable point along the chain, such as ethynyl and propynyl. C_{2-6} Alkynyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, or unsaturated (aromatic). Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. As shown above, bridged rings are also included in the definition of carbocycle (e.g., [2.2.2]bicyclooctane). A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a trycyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

As used herein, the term "heterocycle" or "heterocyclic group" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 ring heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_p$). The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_p$). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Preferred bridges include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a trycyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl,

chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected

from 1, 2-ethanedisulfonic, 2-acetoxybenzoic, 2-hydroxyethanesulfonic, acetic, ascorbic, benzenesulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methanesulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluenesulfonic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p 1445, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that there presently recited compounds do not contain a N-halo, $S(O)_2H$, or S(O)H group.

"Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting it development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit factor Xa. "Therapeutically effective amount" is also intended to include an amount of the combination of compounds claimed that is effective to inhibit factor Xa. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*:27-55, occurs when the effect (in this case, inhibition of factor Xa) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antithrombotic effect, or some other beneficial effect of the combination compared with the individual components.

SYNTHESIS

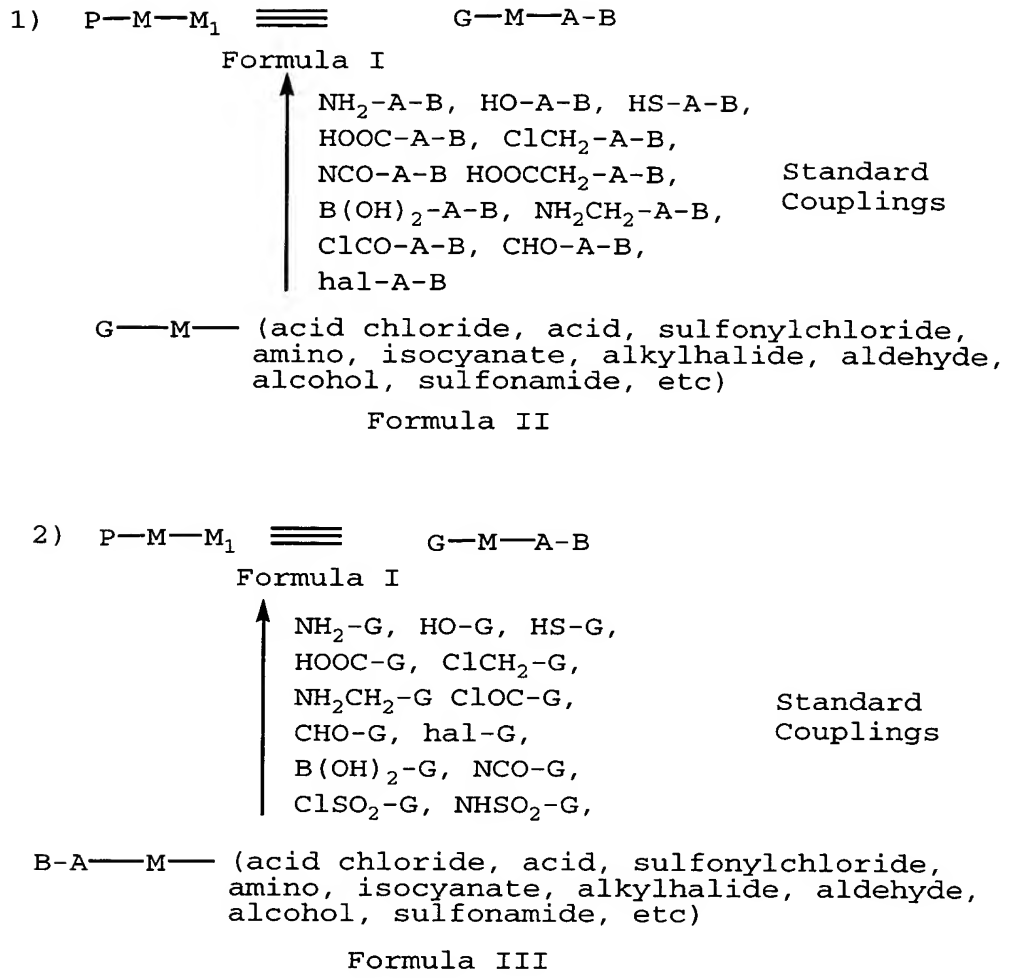
The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present

invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1991). All references cited herein are hereby incorporated in their entirety herein by reference.

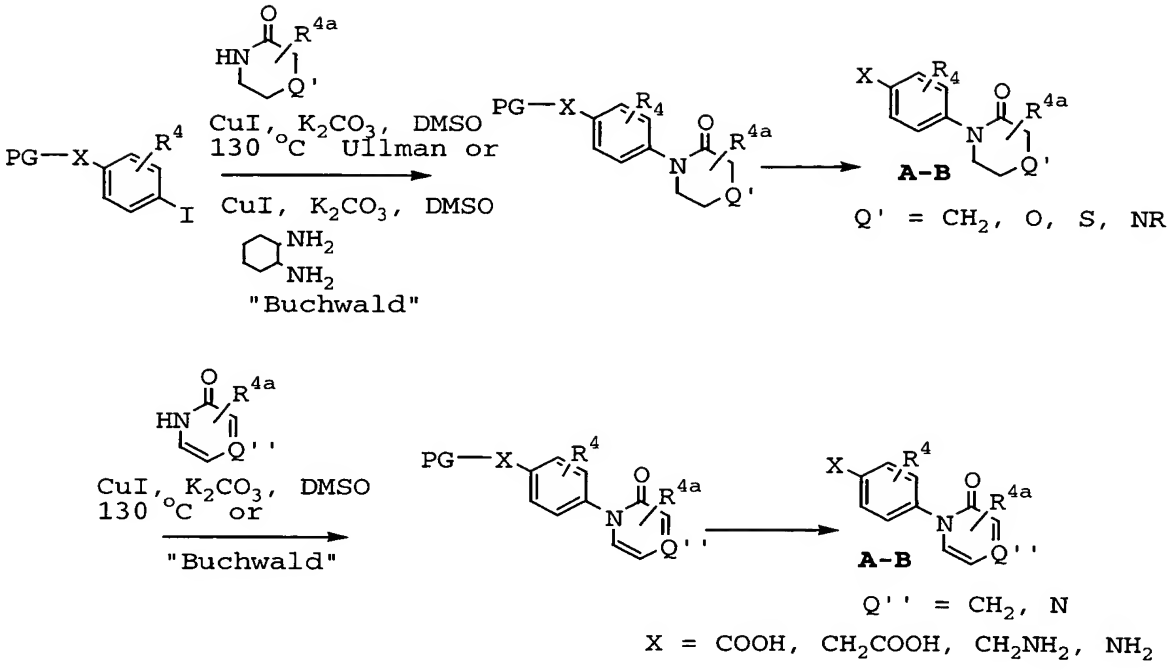
The synthesis of compounds of the present invention that involves the usage of intermediate A-B is accomplished via standard methods known to those skilled in the art. The general route that involves this type of methodology is outlined in Scheme 1. Construction of compounds with general structure G-M-A-B can be performed in two directions: 1) From G to G-M then to G-M-A-B or 2) From A-B to M-A-B then to G-M—A-B. During the synthesis of these compounds, protecting groups to prevent cross-reaction during the coupling conditions optionally protect the functional groups of the substituents. Examples of suitable protecting groups and their uses are described in "The Peptides: analysis, Synthesis, Biology", academic press, Vol.3 (Groii, et. al. Eds., 1981). Functional group transformations and coupling reactions that can be used to prepare compounds of the present invention are described in "Advanced Organic Chemistry: Reaction, Mechanism, and Structure" (March, et. al. fourth Ed.) and "Comprehensive Organic Transformations" (Larock, second Ed.).

Scheme 1



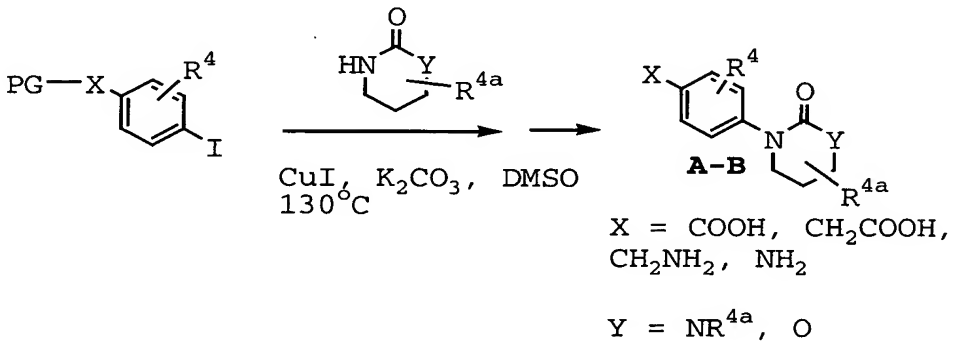
A-B intermediates can be obtained via Ullman reaction or Buchwald modified Ullman reaction (*J. Am. Chem. Soc.* **2001**, *123*, 7727) using CuI and 1,2-cyclohexyldiamine or 1,10-phenanthroline as the catalyst that are outlined in the schemes below.

Scheme 2



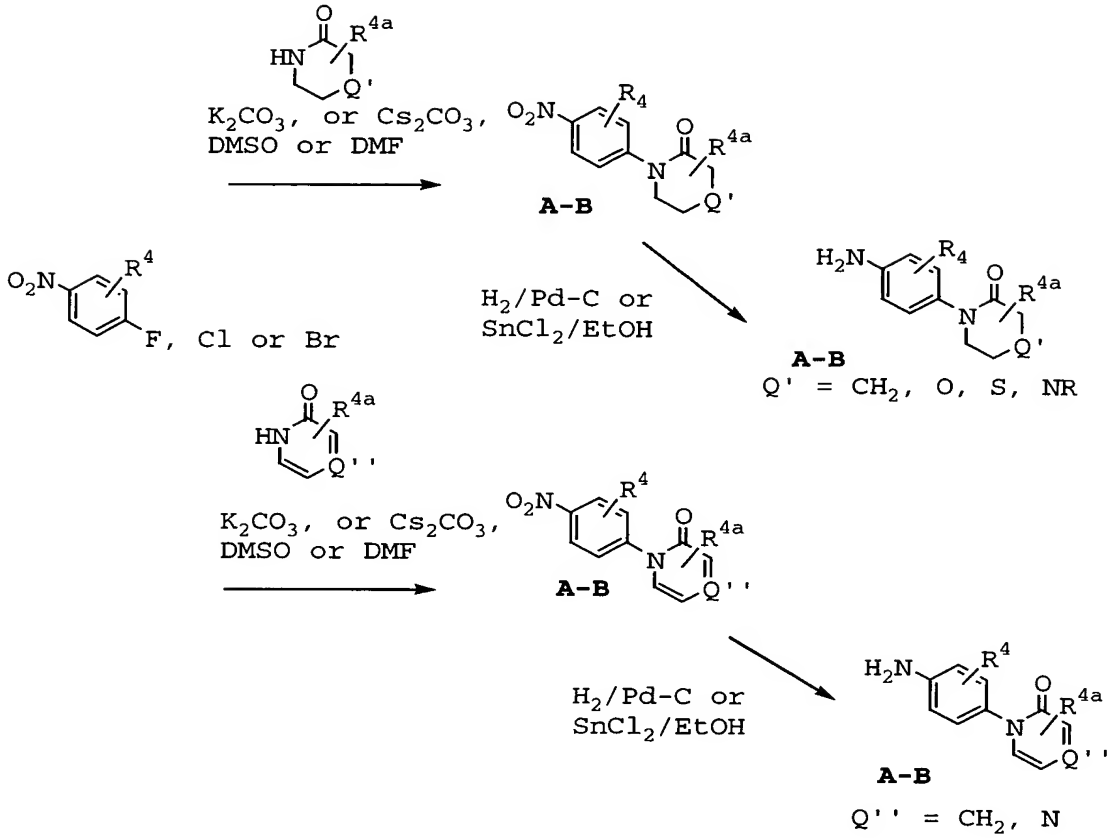
Intermediates A-B wherein the B group contains an oxidizable group can be obtained by oxidation, e.g. S to SO and SO_2. The pyridone analogs can also be prepared via the Ullman methodology. The Ullman coupling can also be applied to prepare cyclic urea or cyclic carbamate analogs as shown in scheme 3.

Scheme 3



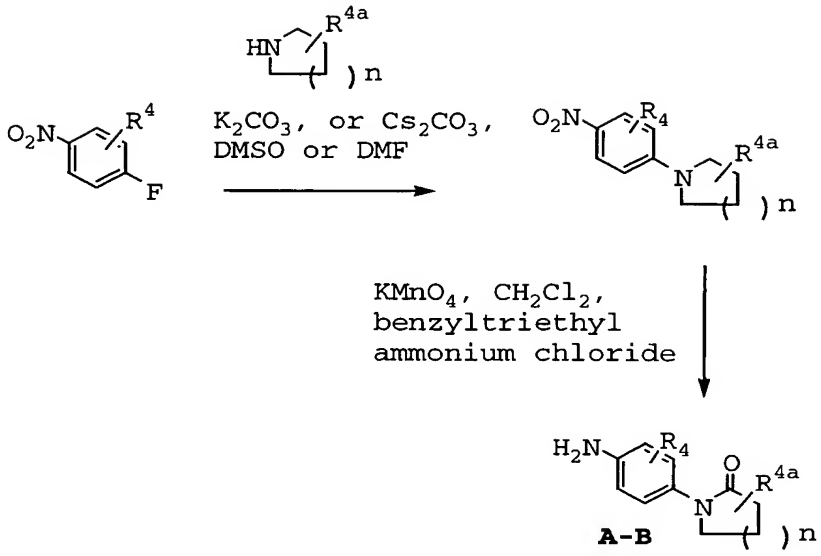
Intermediate A-B can also be prepared via aromatic nucleophile displacement of substituted halo-nitrobenzenes followed by reduction and other transformation as shown in scheme 4.

Scheme 4



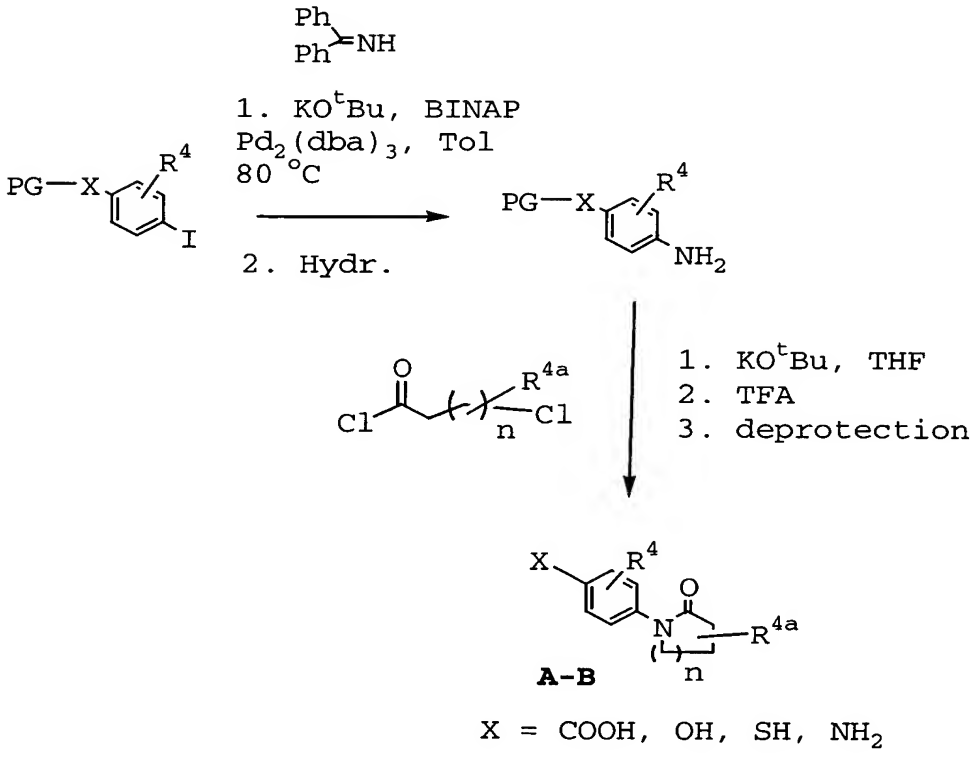
Intermediate A-B can also be prepared via aromatic nucleophilic substitution of fluoronitrobenzenes with the 5-7 membered bases followed by a-carbon oxiadtion with KMnO4 as shown in scheme 5.

Scheme 5



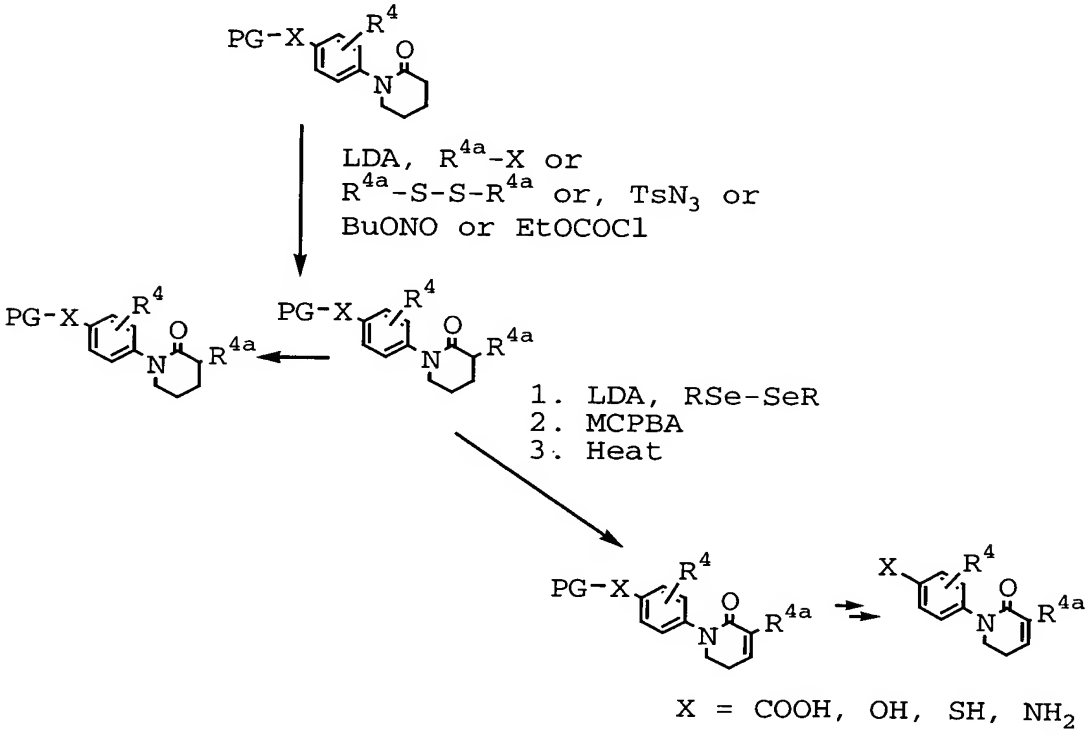
The lactam A-B analogs can also be prepared via the method outlined in scheme 6.

Scheme 6



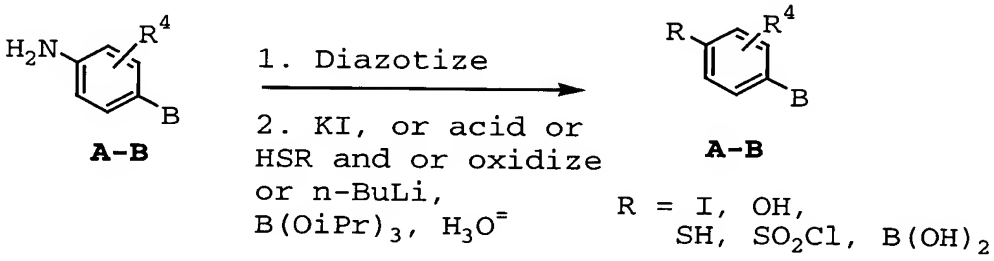
Piperidone A-B intermediates shown above can also be further elaborated to afford other compounds of the present invention by numerous methods known to those skilled in the art (e.g., see scheme 7).

Scheme 7



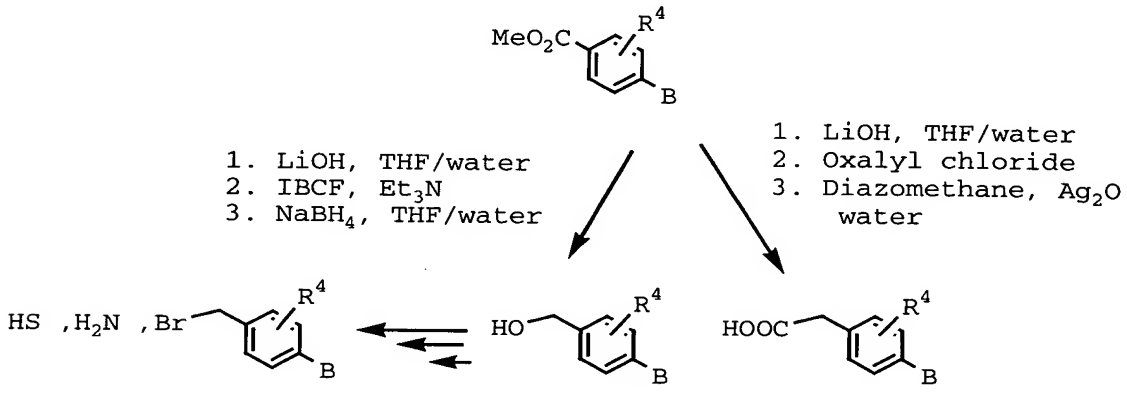
Additional A-B intermediates can be synthesized by the chemical manipulation of the amino functionality of the compounds described above (see Scheme 8).

Scheme 8

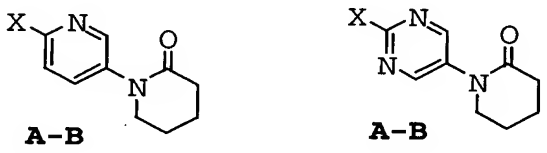


Other possible A-B intermediates can be synthesized by the methods shown in scheme 9 from the carboxylic ester intermediates that can be homologated via the Arndt Eistert methodology. Alternatively, the ester functionality can be reduced to the alcohol that in turn can be converted to a variety of A-B intermediates by procedures known to those skilled in the art.

Scheme 9



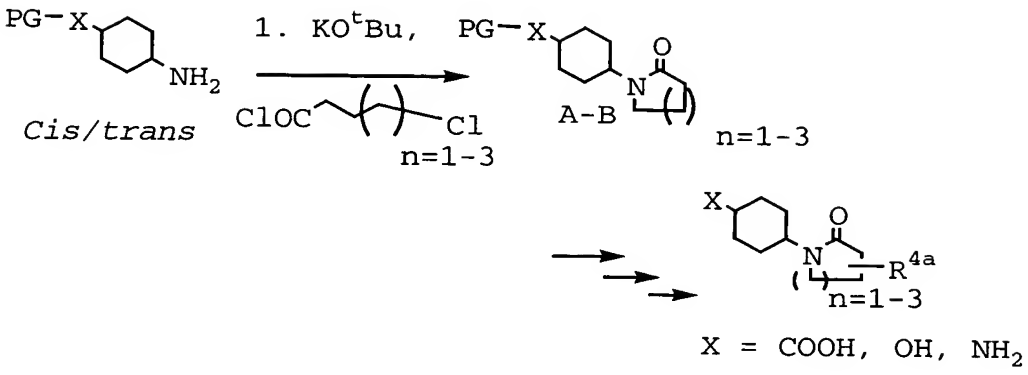
Ortho-substituted pyridyl and pyrimidyl A-B analogs (see structures below) can also be prepared using routes similar to those of scheme 2-9.



X = COOH, NH_2

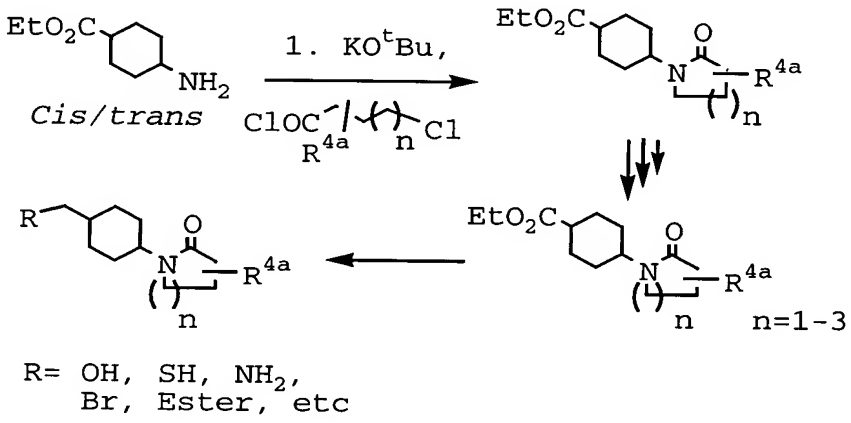
Non-aromatic intermediates as shown in scheme 10 can be synthesized via procedures known to those skilled in the art. These intermediates can then be further manipulated to incorporate R^{4a} via procedures previously described.

Scheme 10



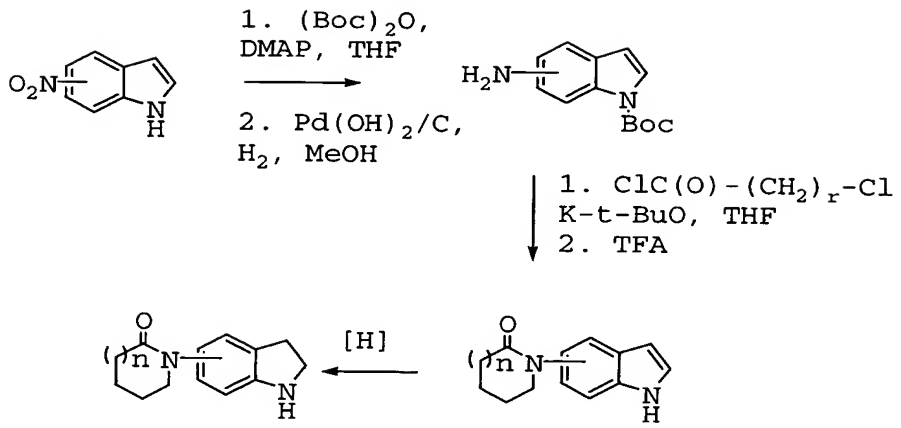
Alternative non-aromatic intermediates can be synthesized via procedures known to those skilled in the art (see scheme 11). These intermediates can also be further manipulated to incorporate R^{4a} via procedures described previously. Further modifications of the ester functionality can be done via procedures described above.

Scheme 11



Intermediates A-B of the present invention wherein A is indoline can be prepared as shown in scheme 12. This type of intermediate can then be attached to the remainder of the desired compound as described previously. Alternatively, the indoline can be attached to the other half of the desired compound prior to formation of the lactam ring.

Scheme 12

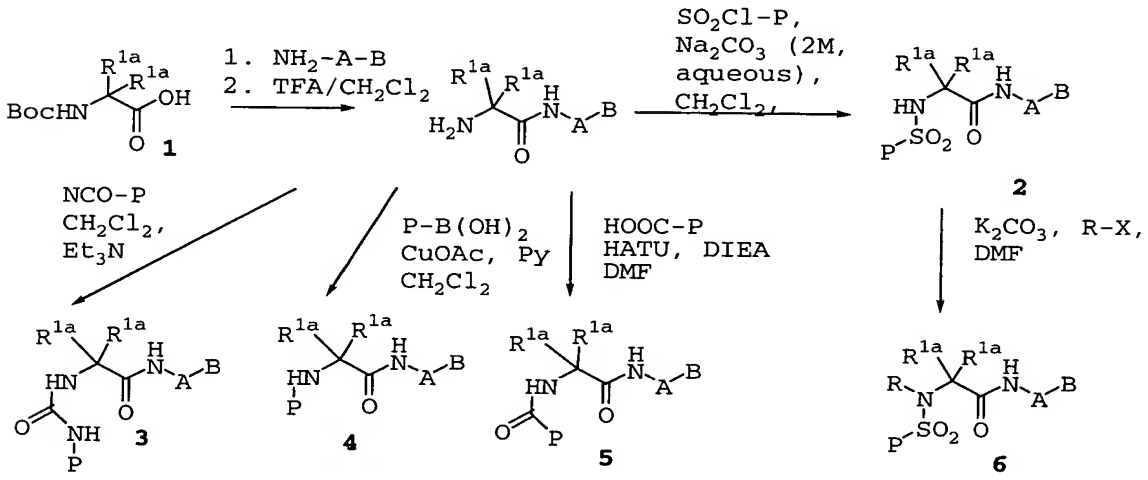


Schemes 2-12 describe how to make the A-B moieties of the present invention and how to couple them to prepare compounds of the present invention.

The functionalized G moiety of the present invention can be prepared using methods known to those of ordinary skill in the art. All of the following patents and publications are incorporated herein by reference. For compounds wherein G is a ring substituted with a basic moiety, one of ordinary skill in the art can look to US 5,939,418, US 5,925,635, US 6,057,342, US 6,187,797, US 6,020,357, US 6,060,491, US 6,191,159, WO98/57951, WO99/32454 WO00/059902, WO01/32628, WO00/39131, USSN 09/892,319, USSN 60/313,552, USSN 60/246,108, USSN 60/246,125, USSN 60/292,665, USSN 60/278,173, and USSN 60/278,165 for starting materials. For compounds wherein G is a ring substituted with a non-basic group, one of ordinary skill in the art can look to US 5,998,424, WO00/39131, WO00/059902, WO01/32628, USSN 09/892,319, USSN 60/313,552, USSN 60/246,108, USSN 60/246,125, USSN 60/292,665, USSN 60/278,173, and USSN 60/278,165 for starting materials. For compounds wherein G is a bicyclic moiety, one of ordinary skill in the art can look to WO98/57951 WO00/039108, WO00/39131, USSN 09/892,319, USSN 60/313,552, USSN 60/246,108, USSN 60/246,125, USSN 60/292,665, USSN 60/278,173, and USSN 60/278,165 for starting materials. For compounds wherein A is an indoline or similar bicycle, one of ordinary skill in the art can look to WO01/005785 for starting materials and intermediates to which the present B group can be coupled or from which the present A-B groups can be formed.

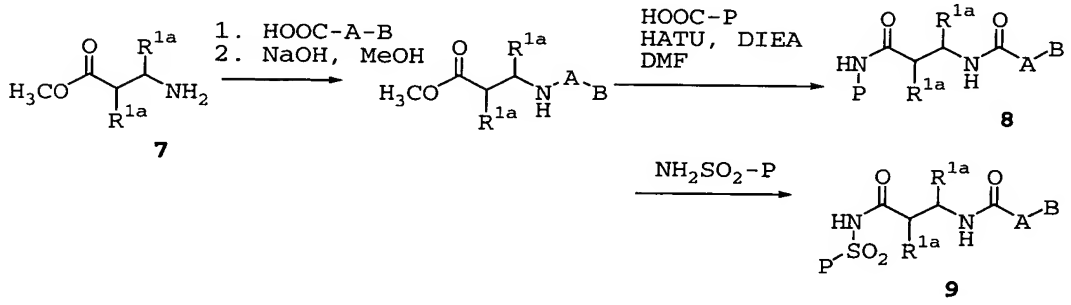
Schemes 13-15 depict several examples for the synthesis of the compounds of formula I of this invention. A properly protected amino acid derivative 1 (naturally or synthetically available) can couple with NH_2-A-B, followed by deprotection and transformations to compounds 2-6 in the present invention.

Scheme 13



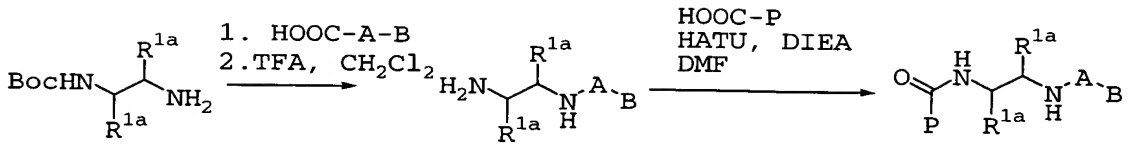
On the other hand, a properly protected β-amino acid derivative 7, can couple with COOH-A-B, followed by deprotaction and transformation to form compounds 8 and 9 in this invention as shown in Scheme 14.

Scheme 14



Similarly, the properly substituted ethylene diamine derivative 10 can couple with COOH-A-B (or ClCO-A-B) to form compounds 11 as illustrated in Scheme 15.

Scheme 15



One stereoisomer of a compound of Formula I may display superior activity compared with the others. Thus, each stereoisomer of a compound of Formula I is considered to be a part of the present invention. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as described in Wilen, S. H. *Tables of Resolving Agents and Optical Resolutions* **1972**, 308 or using enantiomerically pure acids and bases. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Jacobsen, E. *Acc. Chem. Res.* **2000**, *33*, 421-431 or using other enantio- and diastereo-selective reactions and reagents known to one skilled in the art of asymmetric synthesis.

UTILITY

The compounds of this invention are inhibitors of factor Xa and are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals (i.e., factor Xa-associated disorders). In general, a thromboembolic disorder is a circulatory disease caused by blood clots (i.e., diseases involving fibrin formation, platelet activation, and/or platelet aggregation). The term "thromboembolic disorders" as used herein includes arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart. The term "thromboembolic disorders" as used herein also includes specific disorders selected from, but not limited to, unstable angina or other acute coronary syndromes, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, or (f)

other procedures in which blood is exposed to an artificial surface that promotes thrombosis. It is noted that thrombosis includes occlusion (e.g. after a bypass) and reocclusion (e.g., during or after percutaneous transluminal coronary angioplasty). The thromboembolic disorders may result from conditions including but not limited to atherosclerosis, surgery or surgical complications, prolonged immobilization, arterial fibrillation, congenital thrombophilia, cancer, diabetes, effects of medications or hormones, and complications of pregnancy. The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.

The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Diapharma/Chromogenix, West Chester, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nm. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i.

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5% PEG 8000. The Michaelis constant, K_m, for substrate hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM - 1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 min and the velocities (rate of absorbance change vs. time) were measured in the time frame of 25-30 min. The following relationship was used to calculate K_i values:

$$(v_o - v_s)/v_s = I/(K_i\ (1 + S/K_m))$$

where:

v_o is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;

I is the concentration of inhibitor;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate;

K_m is the Michaelis constant.

Compounds tested in the above assay are considered to be active if they exhibit a K_i of $\leq$10 μM. Preferred compounds of the present invention have K_i's of $\leq$1 μM. More preferred compounds of the present invention have K_i's of $\leq$0.1 μM. Even more preferred compounds of the present invention have K_i's of $\leq$0.01 μM. Still more preferred compounds of the present invention have K_i's of $\leq$0.001 μM. Using the methodology described above, a number of compounds of the present invention were found to exhibit K_i's of $\leq$10 μM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing that contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After 40 min, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group. The ID_{50} values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of the present invention may also be useful as inhibitors of serine proteases, notably human thrombin, Factor VIIa, Factor IXa, Factor XIa, urokinase, plasma kallikrein, and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990), herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, was incubated with various substrate concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 min of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm that arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of the reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a K_i of less than 10 μm, thereby confirming the utility of the compounds of the present invention as effective thrombin inhibitors.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of the present invention that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to treat a thromboembolic condition or disease.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. By "administered in combination" or "combination therapy" it is meant that a compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

Additional therapeutic agents include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, thrombolytic or fibrinolytic agents, anti-arrythmic agents, anti-hypertensive agents, calcium channel blockers (L-type and T-type), cardiac glycosides, diruetics, mineralocorticoid receptor antagonists, phospodiesterase inhibitors, cholesterol/lipid lowering agents and lipid profile therapies, anti-diabetic agents, anti-depressants, anti-inflammatory agents (steroidal and non-steroidal), anti-osteoporosis agents, hormone replacement therapies, oral contraceptives, anti-obesity agents, anti-anxiety agents, anti-proliferative agents, anti-tumor agents, anti-ulcer and gastroesophageal reflux disease agents, growth hormone and/or growth hormone secretagogues, thyroid mimetics (including thyroid receptor antagonist), anti-infective agents, anti-viral agents, anti-bacterial agents, and anti-fungal agents.

Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin (either unfractionated heparin or any commercially available low molecular weight heparin), synthetic pentasaccharide, direct acting thrombin inhibitors including hirudin and argatrobanas well as other factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function, for example by inhibiting the aggregation, adhesion or granular secretion of platelets. Agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam, and pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA) and piroxicam are preferred. Other suitable platelet inhibitory agents include IIb/IIIa antagonists (e.g., tirofiban, eptifibatide, and abciximab), thromboxane-A2-receptor antagonists (e.g., ifetroban), thromboxane-A2-synthetase inhibitors, PDE-III inhibitors (e.g., dipyridamole), and pharmaceutically acceptable salts or prodrugs thereof.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, is also intended to include ADP (adenosine diphosphate) receptor antagonists, preferably antagonists of the purinergic receptors P_2Y_1 and P_2Y_{12}, with P_2Y_{12} being even more preferred. Preferred P_2Y_{12} receptor antagonists include ticlopidine and clopidogrel,

including pharmaceutically acceptable salts or prodrugs thereof. Clopidogrel is an even more preferred agent. Ticlopidine and clopidogrel are also preferred compounds since they are known to be gentle on the gastro-intestinal tract in use.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boropeptides, heparins, hirudin, argatroban, and melagatran, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal α-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. The term thrombolytics or fibrinolytic agents (or thrombolytics or fibrinolytics), as used herein, denote agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator (natural or recombinant) and modified forms thereof, anistreplase, urokinase, streptokinase, tenecteplase (TNK), lanoteplase (nPA), factor VIIa inhibitors, PAI-1 inhibitors (i.e., inactivators of tissue plasminogen activator inhibitors), alpha2-antiplasmin inhibitors, and anisoylated plasminogen streptokinase activator complex, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in EP 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Examples of suitable anti-arrythmic agents for use in combination with the present compounds include: Class I agents (such as propafenone); Class II agents (such as carvadiol and propranolol); Class III agents (such as sotalol, dofetilide, amiodarone, azimilide and ibutilide); Class IV agents (such as ditiazem and

verapamil); K^+ channel openers such as I_{Ach} inhibitors, and I_{Kur} inhibitors (e.g., compounds such as those disclosed in WO01/40231).

Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include: alpha adrenergic blockers; beta adrenergic blockers; calcium channel blockers (e.g., diltiazem, verapamil, nifedipine, amlodipine and mybefradil); diruetics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone); renin inhibitors; ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril); AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan); ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265); Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389); neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat, gemopatrilat and nitrates).

Examples of suitable calcium channel blockers (L-type or T-type) for use in combination with the compounds of the present invention include diltiazem, verapamil, nifedipine, amlodipine and mybefradil.

Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

Examples of suitable diruetics for use in combination with the compounds of the present invention include: chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, and spironolactone.

Examples of suitable mineralocorticoid receptor antagonists for use in combination with the compounds of the present invention include sprionolactone and eplirinone.

Examples of suitable phospodiesterase inhibitors for use in combination with the compounds of the present invention include: PDE III inhibitors (such as cilostazol); and PDE V inhibitors (such as sildenafil).

Examples of suitable cholesterol/lipid lowering agents and lipid profile therapies for use in combination with the compounds of the present invention include: HMG-CoA reductase inhibitors (e.g., pravastatin, lovastatin, atorvastatin, simvastatin, fluvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin)); squalene synthetase inhibitors; fibrates; bile acid sequestrants (such as questran); ACAT inhibitors; MTP inhibitors; lipooxygenase inhibitors; choesterol absorption inhibitors; and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include: biguanides (e.g., metformin); glucosidase inhibitors (e.g., acarbose); insulins (including insulin secretagogues or insulin sensitizers); meglitinides (e.g., repaglinide); sulfonylureas (e.g., glimepiride, glyburide and glipizide); biguanide/glyburide combinations (e.g., glucovance), thiozolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in WO00/59506, glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

Examples of suitable anti-depressant agents for use in combination with the compounds of the present invention include nefazodone and sertraline.

Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include: prednisone; dexamethasone; enbrel; protien tyrosine kinase (PTK) inhibitors; cyclooxygenase inhibitors (including NSAIDs, and COX-1 and/or COX-2 inhibitors); aspirin; indomethacin; ibuprofen; prioxicam; naproxen; celecoxib; and/or rofecoxib.

Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate and raloxifene.

Examples of suitable hormone replacement therapies for use in combination with the compounds of the present invention include estrogen (e.g., congugated estrogens) and estradiol.

Examples of suitable anti-coagulants for use in combination with the compounds of the present invention include heparins (e.g., unfractioned and low molecular weight heparins such as enoxaparin and dalteparin).

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include orlistat and aP2 inhibitors (such as those disclosed in WO00/59506).

Examples of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, and hydroxyzine pamoate.

Examples of suitable anti-proliferative agents for use in combination with the compounds of the present invention include cyclosporin A, paclitaxel, adriamycin; epithilones, cisplatin, and carboplatin.

Examples of suitable anti-ulcer and gastroesophageal reflux disease agents for use in combination with the compounds of the present invention include famotidine, ranitidine, and omeprazole.

Administration of the compounds of the present invention (i.e., a first therapeutic agent) in combination with at least one additional therapeutic agent (i.e., a second therapeutic agent), preferably affords an efficacy advantage over the compounds and agents alone, preferably while permitting the use of lower doses of each (i.e., a synergistic combination). A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety. It is preferred that at least one of the therapeutic agents is administered in a sub-therapeutic dose. It is even more preferred that all of the therapeutic agents be administered in sub-therapeutic doses. Sub-therapeutic is intended to mean an amount of a therapeutic agent that by itself does not give the desired therapeutic effect for the condition or disease being treated. Synergistic combination is intended to mean that the observed effect of the combination is greater than the sum of the individual agents administered alone.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the

reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude factor Xa was present.

Compounds of the present invention may further be useful as diagnostic agents and adjuncts. For example, the present compounds may be useful in maintaining whole and fractionated blood in the fluid phase such as required for analytical and biological testing.

The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment of a thromboembolic disorder (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent to treat a thromboembolic disorder. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube (e.g., for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (e.g., cardboard or plastic), crates, cartons, bags (e.g., paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (e.g., the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (e.g., paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (e.g., printed or applied).

Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic

characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/min during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars

such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl-or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, a standard reference text in this field.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of the present invention are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Where the compounds of Formula I are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

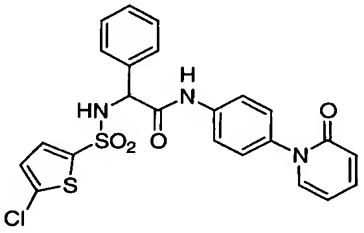
These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are afforded for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Example 1

2-(5-Chloro-thiophene-2-sulfonylamino)-*N*-[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide



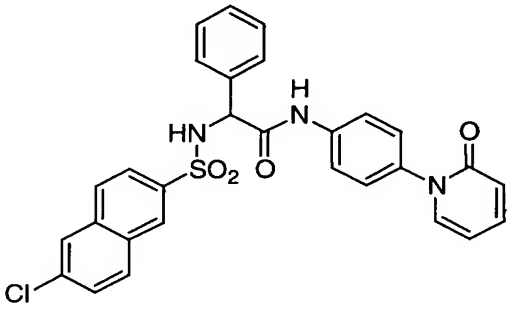
Part A. 1-(4-Aminophenyl)-1*H*-pyridin-2-one (0.59 g, 3.19 mmol) and Boc-DL-PHG-OH (0.80 g, 3.19 mmol) were stirred in dry DMF (8 mL) at RT under N_2. HATU (1.33 g, 3.51 mmol, 1.1 eq) was added, followed by the addition of DIEA (1.12 g, 6.38 mmol, 2.0 eq). The resulting mixture was stirred at rt for 3h. H_2O was added, and the mixture was extracted with EtOAc (2x), washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2, then CH_2Cl_2:EtOAc = 1:1) to give {[4-(2-oxo-2*H*-pyridin-1-yl)phenylcarbamoyl]phenylmethyl}-carbamic acid *tert*-butyl ester (1.23 g, yield: 92%). LC/MS-ESI $(M+H)^+$ 420.4.

Part B. The product from Part A (500 mg, 1.19 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (5 mL) was added. The mixture was stirred at rt for 1h. LC/MS showed completion of the reaction. The residue was dried in *vacuo*. The residue (30 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (0.5 mL). 2M aqueous Na_2CO_3 (0.1 ml, 0.2 mmol) was added, followed by 5-chloro-2-thiophenesulfonyl chloride (in excess). The mixture was stirred at rt for 2h. LC/MS showed completion of the reaction. It was extracted with EtOAc, washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by FCC (silica gel, CH_2Cl_2, then CH_2Cl_2:EtOAc=1:1 to 0:1) to give pure 2-(5-chloro-thiophene-2-sulfonylamino)-*N*-

[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide (19 mg, yield: 42%). LC/MS ESI $(M+H)^+$ 500.2.

Example 2

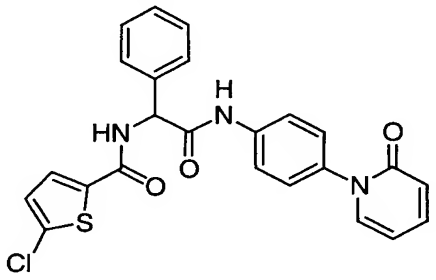
2-(6-Chloro-naphthalene-2-sulfonylamino)-*N*-[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI $(M+H)^+$ 544.2.

Example 3

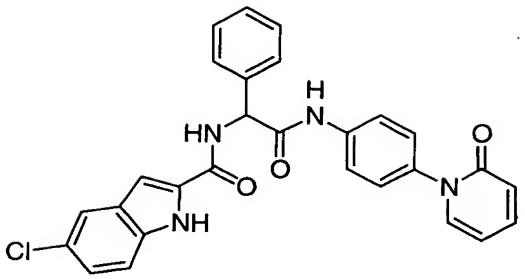
5-Chloro-thiophene-2-carboxylic acid {[4-(2-oxo-*2H*-pyridin-1-yl)-phenylcarbamoyl]-phenyl-methyl}-amide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI $(M+H)^+$ 464.4.

Example 4

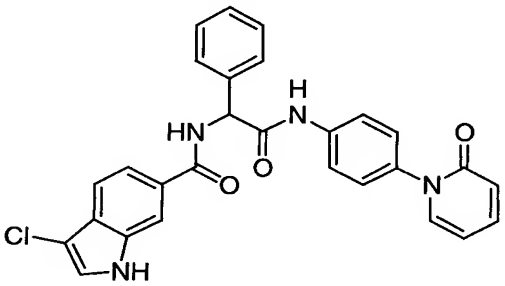
5-Chloro-1*H*-indole-2-carboxylic acid {[4-(2-oxo-2*H*-pyridin-1-yl)-phenylcarbamoyl]-phenyl-methyl}-amide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI $(M+H)^+$ 497.6.

Example 5

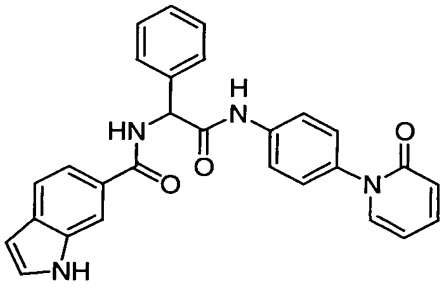
3-Chloro-1*H*-indole-6-carboxylic acid {[4-(2-oxo-2*H*-pyridin-1-yl)-phenylcarbamoyl]-phenyl-methyl}-amide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI $(M+H)^+$ 497.6.

Example 6

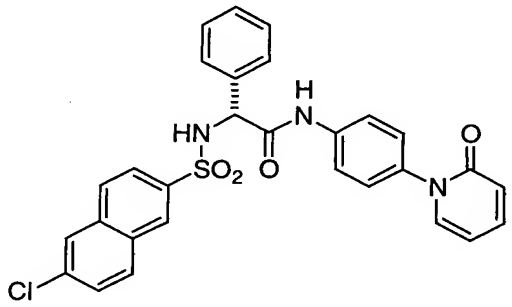
1*H*-Indole-6-carboxylic acid {[4-(2-oxo-2*H*-pyridin-1-yl)-phenylcarbamoyl]-phenyl-methyl}-amide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI $(M+H)^+$ 463.2.

Example 7

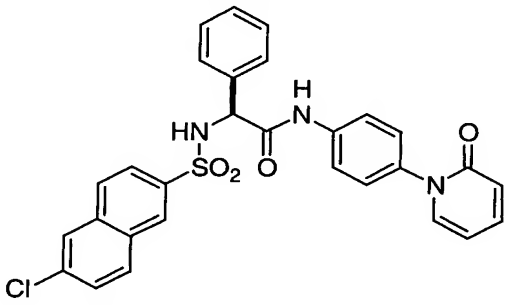
2-*R*-(6-Chloro-naphthalene-2-sulfonylamino)-*N*-[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI $(M+H)^+$ 544.6.

Example 8

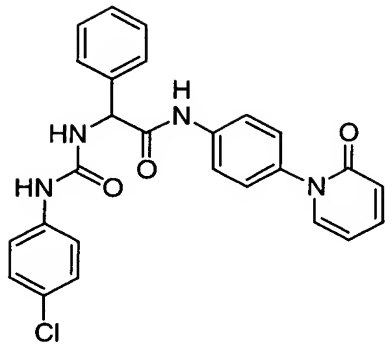
2-*S*-(6-Chloro-naphthalene-2-sulfonylamino)-*N*-[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide



Following a procedure analogous to that described in Example 1, the title compounds. LC/MS ESI $(M+H)^+$ 544.6.

Example 9

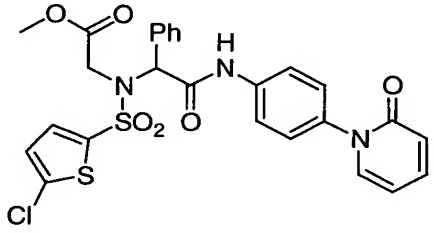
2-[3-(4-Chloro-phenyl)-ureido]-*N*-[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide



Following a procedure analogous to that described in Example 1, the title compounds. LC/MS ESI $(M+H)^+$ 473.6.

Example 10

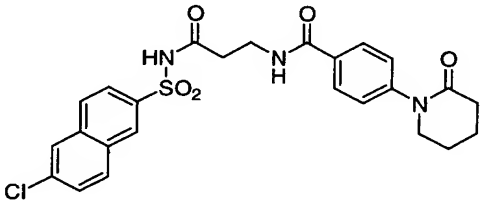
2-(5-Chloro-thiophene-2-sulfonylamino)-*N*-[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]-2-phenyl-acetamide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI $(M+H)^+$ 573.5.

Example 11

N-β-(6-chloro-naphthalene-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide



Step A. To a solution of 4-(2-oxo-piperidin-1-yl) benzoic acid (219.0 mg, 1.0 mmol), β-alanine methyl ester, hydrochloride (154 mg, 1.1 mmol), HATU (418 mg, 1.1 mmol), and HOBt (149 mg, 1.1 mmol) in DMF at 0°C was added DIEA (0.87 ml, 5 mmol) dropwise. The mixture was stirred at 0°C for 30 min and rt for 4 hr. Most of

the solvent was evaporated, and the residue was diluted with EtOAc. The mixture was washed with water, 1N HCl, $NaHCO_3$, and brine. Reverse phase HPLC purification (20% CH_3CN/H_2O, 40 ml/min) yielded the desired 3-[4-(2-oxo-piperidin-1-yl)-benzoylamino]-propionic acid methyl ester as a white solid. MS found: 305.3 $(M+1)^+$.

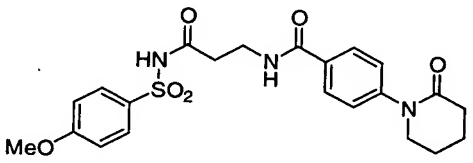
Step B. To a solution of the product from Step A (153 mg, 0.5 mmol) in THF/water (1:1) at 0°C was added 2N LiOH solution (1.5 mL). The mixture was stirred at 0°C for 30 min and rt for 2h. After being acidified with 1N HCl solution to pH = 3, the solvent was evaporated and the residue was purified by reverse phase HPLC. The desired 3-[4-(2-oxo-piperidin-yl)-benzoylamino]-propionic acid was obtained as a white solid. MS found: 291.3 $(M+1)^+$.

Step C. 6-Chloro-naphthalene-2-sulfonyl chloride (261 mg, 1 mmol) was treated with excess ammonia in methanol. The mixture was stirred at room temperature for 2 hr. The solvent was evaporated and the residue dried on vacuum to yield the desired sulfonamide as white solid. MS found: 242.0 $(M+1)^+$.

Step D. To a solution of the products obtained from steps B (145 mg, 0.5 mmol) and C (124 mg, 0.5 mmol) in CH_2Cl_2 were added EDCI (119 mg, 0.6 mmol) and DMAP (25 mg, 0.2 mmol). The resulting mixture was stirred at rt under N_2 over night. The mixture was washed with water and purified by reverse phase HPLC. The desired N-b-(6-chloro-naphthalene-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide was obtained as white solid. MS found: 514.2 $(M+)^+$.

Example 12

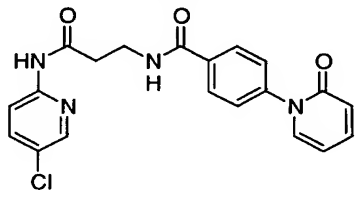
N-[β-(4-methoxyl-benzenesulfonylamino)-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)benzamide



Following a procedure analogous to that described in Example 1, the title compound was obtained as white solid. MS found: $(M+1)^+ = 460.2$.

Example 13

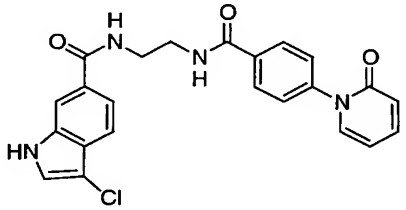
_N_-[2-(5-Chloro-pyridin-2-ylcarbamoyl)ethyl]-4-(2-oxo-2_H_-pyridin-1-yl)benzamide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI 397.2 $(M+H)^+$.

Example 14

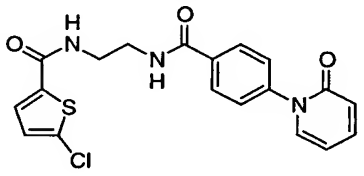
3-Chloro-1_H_-indole-6-carboxylic acid {2-[4-(2-oxo-2_H_-pyridin-1-yl)benzoylamino]ethyl}amide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI$(M+H)^+$ 435.6.

Example 15

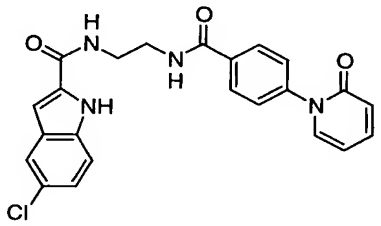
5-Chloro-thiophene-2-carboxylic acid {2-[4-(2-oxo-2_H_-pyridin-1-yl)benzoylamino]ethyl}amide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI $(M+H)^+$ 402.6.

Example 16

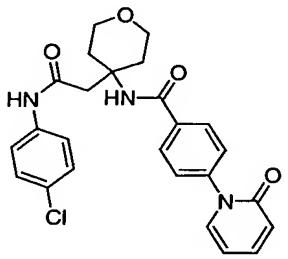
5-Chloro-1*H*-indole-2-carboxylic acid {2-[4-(2-oxo-2*H*-pyridin-1-yl)benzoylamino]ethyl}amide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI $(M+H)^+$ 435.6.

Example 17

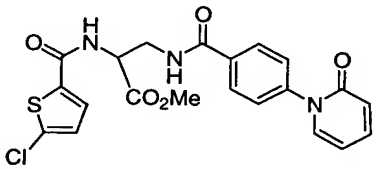
N-{4-[(4-Chloro-phenylcarbamoyl)-methyl]-tetrahydro-pyran-4-yl}-4-(2-oxo-2H-pyridin-1-yl)-benzamide



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI $(M+H)^+$ 466.4.

Example 18

2-[(5-Chloro-thiophene-2-carbonyl)-amino]-3-[4-(2-oxo-2H-pyridin-1-yl)-benzoylamino]-propionic acid methyl ester



Following a procedure analogous to that described in Example 1, the title compound was obtained. LC/MS ESI $(M+H)^+$ 460.2.

Examples 19-454, shown in Table 1 below, can be made using procedures similar to those of Examples 1-18.

Table 1

Example	Name
19.	3-chloro-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}ethyl)-1*H*-indole-6-carboxamide
20.	5-chloro-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}ethyl)thiophene-2-carboxamide
21.	5-methoxy-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}ethyl)thiophene-2-carboxamide
22.	3-chloro-5-methoxy-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}ethyl)thiophene-2-carboxamide
23.	3,5-dichloro-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}ethyl)thiophene-2-carboxamide
24.	5-chloro-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
25.	5-chloro-*N*-(3-methyl-2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}butyl)thiophene-2-carboxamide
26.	5-chloro-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}-2-phenylethyl)thiophene-2-carboxamide
27.	5-chloro-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}-3-phenylpropyl)thiophene-2-carboxamide
28.	methyl 3-{[(5-chloro-2-thienyl)carbonyl]amino}-*N*-[4-(2-oxopiperidin-1-yl)benzoyl]alaninate
29.	3-{[(5-chloro-2-thienyl)carbonyl]amino}-*N*-[4-(2-oxopiperidin-1-yl)benzoyl]alanine
30.	methyl 4-{[(5-chloro-2-thienyl)carbonyl]amino}-3-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}butanoate
31.	4-{[(5-chloro-2-thienyl)carbonyl]amino}-3-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}butanoic acid
32.	*N*-{3-[(4-chlorophenyl)amino]-1-methyl-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
33.	*N*-{3-[(4-chlorophenyl)amino]-3-oxo-1-phenylpropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
34.	*N*-{1-benzyl-3-[(4-chlorophenyl)amino]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
35.	5-[(4-chlorophenyl)amino]-5-oxo-3-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}pentanoic acid
36.	N^4-(4-chlorophenyl)-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]asparagine

37.	6-[(4-chlorophenyl)amino]-6-oxo-4-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}hexanoic acid
38.	N^4-(4-chlorophenyl)-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
39.	N^4-(4-chlorophenyl)-N^1,N^1-dimethyl-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
40.	*N*-{3-[(4-chlorophenyl)amino]-1-[(dimethylamino)methyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
41.	*N*-{3-[(4-chlorophenyl)amino]-1-[(methylamino)methyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
42.	*N*-{1-(aminomethyl)-3-[(4-chlorophenyl)amino]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
43.	*N*-{1-[(acetylamino)methyl]-3-[(4-chlorophenyl)amino]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
44.	*N*-[3-[(4-chlorophenyl)amino]-1-({[(methylamino)carbonyl]amino}methyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
45.	*N*-(3-[(4-chlorophenyl)amino]-1-{[(methylsulfonyl)amino]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-yl)benzamide
46.	*N*-[3-[(4-chlorophenyl)amino]-1-(hydroxymethyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
47.	*N*-{3-[(4-chlorophenyl)amino]-1-[(2-methoxyethoxy)methyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
48.	*N*-[3-[(4-chlorophenyl)amino]-1-(methoxymethyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
49.	*N*-(3-[(4-chlorophenyl)amino]-1-{[2-(dimethylamino)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-yl)benzamide
50.	N^4-(4-chlorophenyl)-N^1-[2-(dimethylamino)ethyl]-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
51.	N^4-(4-chlorophenyl)-N^1-(2-morpholin-4-ylethyl)-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
52.	N^4-(4-chlorophenyl)-N^1-[2-(1,1-dioxidothiomorpholin-4-yl)ethyl]-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
53.	N^4-(4-chlorophenyl)-N^1-[2-(4-methylpiperazin-1-yl)ethyl]-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
54.	*N*-[3-[(4-chlorophenyl)amino]-1-({[2-(4-methylpiperazin-1-yl)ethyl]amino}methyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
55.	*N*-[3-[(4-chlorophenyl)amino]-1-({methyl[2-(4-methylpiperazin-1-yl)ethyl]amino}methyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
56.	*N*-(3-[(4-chlorophenyl)amino]-1-{[methyl(2-morpholin-4-ylethyl)amino]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-yl)benzamide
57.	*N*-(3-[(4-chlorophenyl)amino]-1-{[[2-(1,1-dioxidothiomorpholin-4-yl)ethyl](methyl)amino]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-

	yl)benzamide
58.	*N*-(3-[(4-chlorophenyl)amino]-1-{[2-(1,1-dioxidothiomorpholin-4-yl)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-yl)benzamide
59.	*N*-{3-[(4-chlorophenyl)amino]-1-[(2-morpholin-4-ylethoxy)methyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
60.	*N*-(3-[(4-chlorophenyl)amino]-1-{[2-(4-methylpiperazin-1-yl)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-yl)benzamide
61.	*N*-[3-[(4-chlorophenyl)amino]-3-oxo-1-(pyrrolidin-1-ylcarbonyl)propyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
62.	*N*-[3-[(4-chlorophenyl)amino]-3-oxo-1-(piperidin-1-ylcarbonyl)propyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
63.	*N*-[3-[(4-chlorophenyl)amino]-1-(morpholin-4-ylcarbonyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
64.	*N*-{3-[(4-chlorophenyl)amino]-1-[(4-methylpiperazin-1-yl)carbonyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
65.	*N*-{3-[(4-chlorophenyl)amino]-1-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
66.	*N*-[3-[(4-chlorophenyl)amino]-1-(morpholin-4-ylmethyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
67.	*N*-[3-[(4-chlorophenyl)amino]-3-oxo-1-(pyrrolidin-1-ylmethyl)propyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
68.	*N*-{3-[(4-chlorophenyl)amino]-3-oxo-1-[(2-oxopyrrolidin-1-yl)methyl]propyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
69.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-methyl-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
70.	*N*-{3-[(5-chloropyridin-2-yl)amino]-3-oxo-1-phenylpropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
71.	*N*-{1-benzyl-3-[(5-chloropyridin-2-yl)amino]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
72.	5-[(5-chloropyridin-2-yl)amino]-5-oxo-3-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}pentanoic acid
73.	N^4-(5-chloropyridin-2-yl)-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]asparagine
74.	6-[(5-chloropyridin-2-yl)amino]-6-oxo-4-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}hexanoic acid
75.	N^4-(5-chloropyridin-2-yl)-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
76.	N^4-(5-chloropyridin-2-yl)-N^1,N^1-dimethyl-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
77.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(dimethylamino)methyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
78.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(methylamino)methyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide

79.	*N*-{1-(aminomethyl)-3-[(5-chloropyridin-2-yl)amino]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
80.	*N*-{1-[(acetylamino)methyl]-3-[(5-chloropyridin-2-yl)amino]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
81.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-({[(methylamino)carbonyl]amino}methyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
82.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[(methylsulfonyl)amino]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-yl)benzamide
83.	*N*-[3-[(5-chloropyridin-2-yl]-1-(hydroxymethyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
84.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(2-methoxyethoxy)methyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
85.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-(methoxymethyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
86.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[2-(dimethylamino)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-yl)benzamide
87.	N^4-(5-chloropyridin-2-yl)-N^1-[2-(dimethylamino)ethyl]-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
88.	N^4-(5-chloropyridin-2-yl)-N^1-(2-morpholin-4-ylethyl)-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
89.	N^4-(5-chloropyridin-2-yl)-N^1-[2-(1,1-dioxidothiomorpholin-4-yl)ethyl]-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
90.	N^4-(5-chloropyridin-2-yl)-N^1-[2-(4-methylpiperazin-1-yl)ethyl]-N^2-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]aspartamide
91.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-({[2-(4-methylpiperazin-1-yl)ethyl]amino}methyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
92.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-({methyl[2-(4-methylpiperazin-1-yl)ethyl]amino}methyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
93.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[methyl(2-morpholin-4-ylethyl)amino]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-yl)benzamide
94.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[[2-(1,1-dioxidothiomorpholin-4-yl)ethyl](methyl)amino]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-yl)benzamide
95.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[2-(1,1-dioxidothiomorpholin-4-yl)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-yl)benzamide
96.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(2-morpholin-4-ylethoxy)methyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
97.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[2-(4-methylpiperazin-1-yl)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopyridin-1(2*H*)-yl)benzamide
98.	*N*-[3-[(5-chloropyridin-2-yl)amino]-3-oxo-1-(pyrrolidin-1-ylcarbonyl)propyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide

99.	*N*-[3-[(5-chloropyridin-2-yl)amino]-3-oxo-1-(piperidin-1-ylcarbonyl)propyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
100.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-(morpholin-4-ylcarbonyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
101.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(4-methylpiperazin-1-yl)carbonyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
102.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
103.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-(morpholin-4-ylmethyl)-3-oxopropyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
104.	*N*-[3-[(5-chloropyridin-2-yl)amino]-3-oxo-1-(pyrrolidin-1-ylmethyl)propyl]-4-(2-oxopyridin-1(2*H*)-yl)benzamide
105.	*N*-{3-[(5-chloropyridin-2-yl)amino]-3-oxo-1-[(2-oxopyrrolidin-1-yl)methyl]propyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
106.	*N*-{3-[(4-chlorophenyl)amino]-2-methyl-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
107.	*N*-{3-[(4-chlorophenyl)amino]-3-oxo-2-phenylpropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
108.	*N*-{2-benzyl-3-[(4-chlorophenyl)amino]-3-oxopropyl}-4-(2-oxopyridin-1(2*H*)-yl)benzamide
109.	*N*-{3-[(4-chlorophenyl)amino]-1-methyl-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
110.	*N*-{3-[(4-chlorophenyl)amino]-3-oxo-1-phenylpropyl}-4-(2-oxopiperidin-1-yl)benzamide
111.	*N*-{1-benzyl-3-[(4-chlorophenyl)amino]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
112.	5-[(4-chlorophenyl)amino]-5-oxo-3-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}pentanoic acid
113.	N^4-(4-chlorophenyl)-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]asparagine
114.	6-[(4-chlorophenyl)amino]-6-oxo-4-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}hexanoic acid
115.	N^4-(4-chlorophenyl)-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]aspartamide
116.	N^4-(4-chlorophenyl)-N^1,N^1-dimethyl-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]aspartamide
117.	*N*-{3-[(4-chlorophenyl)amino]-1-[(dimethylamino)methyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
118.	*N*-{3-[(4-chlorophenyl)amino]-1-[(methylamino)methyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
119.	*N*-{1-(aminomethyl)-3-[(4-chlorophenyl)amino]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
120.	*N*-{1-[(acetylamino)methyl]-3-[(4-chlorophenyl)amino]-3-oxopropyl}-4-(2-

	oxopiperidin-1-yl)benzamide
121.	*N*-[3-[(4-chlorophenyl)amino]-1-({[(methylamino)carbonyl]amino}methyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
122.	*N*-(3-[(4-chlorophenyl)amino]-1-{[(methylsulfonyl)amino]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
123.	*N*-[3-[(4-chlorophenyl)amino]-1-(hydroxymethyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
124.	*N*-{3-[(4-chlorophenyl)amino]-1-[(2-methoxyethoxy)methyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
125.	*N*-[3-[(4-chlorophenyl)amino]-1-(methoxymethyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
126.	*N*-(3-[(4-chlorophenyl)amino]-1-{[2-(dimethylamino)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
127.	N^4-(4-chlorophenyl)-N^1-[2-(dimethylamino)ethyl]-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]aspartamide
128.	N^4-(4-chlorophenyl)-N^1-(2-morpholin-4-ylethyl)-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]aspartamide
129.	N^4-(4-chlorophenyl)-N^1-[2-(1,1-dioxidothiomorpholin-4-yl)ethyl]-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]aspartamide
130.	N^4-(4-chlorophenyl)-N^1-[2-(4-methylpiperazin-1-yl)ethyl]-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]aspartamide
131.	*N*-[3-[(4-chlorophenyl)amino]-1-({[2-(4-methylpiperazin-1-yl)ethyl]amino}methyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
132.	*N*-[3-[(4-chlorophenyl)amino]-1-({methyl[2-(4-methylpiperazin-1-yl)ethyl]amino}methyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
133.	*N*-(3-[(4-chlorophenyl)amino]-1-{[methyl(2-morpholin-4-ylethyl)amino]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
134.	*N*-(3-[(4-chlorophenyl)amino]-1-{[[2-(1,1-dioxidothiomorpholin-4-yl)ethyl](methyl)amino]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
135.	*N*-(3-[(4-chlorophenyl)amino]-1-{[2-(1,1-dioxidothiomorpholin-4-yl)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
136.	*N*-{3-[(4-chlorophenyl)amino]-1-[(2-morpholin-4-ylethoxy)methyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
137.	*N*-(3-[(4-chlorophenyl)amino]-1-{[2-(4-methylpiperazin-1-yl)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
138.	*N*-[3-[(4-chlorophenyl)amino]-3-oxo-1-(pyrrolidin-1-ylcarbonyl)propyl]-4-(2-oxopiperidin-1-yl)benzamide
139.	*N*-[3-[(4-chlorophenyl)amino]-3-oxo-1-(piperidin-1-ylcarbonyl)propyl]-4-(2-oxopiperidin-1-yl)benzamide
140.	*N*-[3-[(4-chlorophenyl)amino]-1-(morpholin-4-ylcarbonyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide

141.	*N*-{3-[(4-chlorophenyl)amino]-1-[(4-methylpiperazin-1-yl)carbonyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
142.	*N*-{3-[(4-chlorophenyl)amino]-1-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
143.	*N*-[3-[(4-chlorophenyl)amino]-1-(morpholin-4-ylmethyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
144.	*N*-[3-[(4-chlorophenyl)amino]-3-oxo-1-(pyrrolidin-1-ylmethyl)propyl]-4-(2-oxopiperidin-1-yl)benzamide
145.	*N*-{3-[(4-chlorophenyl)amino]-3-oxo-1-[(2-oxopyrrolidin-1-yl)methyl]propyl}-4-(2-oxopiperidin-1-yl)benzamide
146.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-methyl-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
147.	*N*-{3-[(5-chloropyridin-2-yl)amino]-3-oxo-1-phenylpropyl}-4-(2-oxopiperidin-1-yl)benzamide
148.	*N*-{1-benzyl-3-[(5-chloropyridin-2-yl)amino]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
149.	5-[(5-chloropyridin-2-yl)amino]-5-oxo-3-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}pentanoic acid
150.	N^4-(5-chloropyridin-2-yl)-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]asparagine
151.	6-[(5-chloropyridin-2-yl)amino]-6-oxo-4-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}hexanoic acid
152.	N^4-(5-chloropyridin-2-yl)-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]aspartamide
153.	N^4-(5-chloropyridin-2-yl)-N^1,N^1-dimethyl-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]aspartamide
154.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(dimethylamino)methyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
155.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(methylamino)methyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
156.	*N*-{1-(aminomethyl)-3-[(5-chloropyridin-2-yl)amino]-3-oxopropyl}-4-(2-oxopiperidin-1-yl benzamide
157.	*N*-{1-[(acetylamino)methyl]-3-[(5-chloropyridin-2-yl)amino]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
158.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-({[(methylamino)carbonyl]amino}methyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
159.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[(methylsulfonyl)amino]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
160.	*N*-[3-[(5-chloropyridin-2-yl]-1-(hydroxymethyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
161.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(2-methoxyethoxy)methyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide

162.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-(methoxymethyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
163.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[2-(dimethylamino)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
164.	N^4-(5-chloropyridin-2-yl)-N^1-[2-(dimethylamino)ethyl]-N^2-[4-(2-oxopiperidin-1-yl benzoyl]aspartamide
165.	N^4-(5-chloropyridin-2-yl)-N^1-(2-morpholin-4-ylethyl)-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]aspartamide
166.	N^4-(5-chloropyridin-2-yl)-N^1-[2-(1,1-dioxidothiomorpholin-4-yl)ethyl]-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]aspartamide
167.	N^4-(5-chloropyridin-2-yl)-N^1-[2-(4-methylpiperazin-1-yl)ethyl]-N^2-[4-(2-oxopiperidin-1-yl)benzoyl]aspartamide
168.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-({[2-(4-methylpiperazin-1-yl)ethyl]amino}methyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
169.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-({methyl[2-(4-methylpiperazin-1-yl)ethyl]amino}methyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
170.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[methyl(2-morpholin-4-ylethyl)amino]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
171.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[[2-(1,1-dioxidothiomorpholin-4-yl)ethyl](methyl)amino]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
172.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[2-(1,1-dioxidothiomorpholin-4-yl)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
173.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(2-morpholin-4-ylethoxy)methyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
174.	*N*-(3-[(5-chloropyridin-2-yl)amino]-1-{[2-(4-methylpiperazin-1-yl)ethoxy]methyl}-3-oxopropyl)-4-(2-oxopiperidin-1-yl)benzamide
175.	*N*-[3-[(5-chloropyridin-2-yl)amino]-3-oxo-1-(pyrrolidin-1-ylcarbonyl)propyl]-4-(2-oxopiperidin-1-yl)benzamide
176.	*N*-[3-[(5-chloropyridin-2-yl)amino]-3-oxo-1-(piperidin-1-ylcarbonyl)propyl]-4-(2-oxopiperidin-1-yl)benzamide
177.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-(morpholin-4-ylcarbonyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
178.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(4-methylpiperazin-1-yl)carbonyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
179.	*N*-{3-[(5-chloropyridin-2-yl)amino]-1-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
180.	*N*-[3-[(5-chloropyridin-2-yl)amino]-1-(morpholin-4-ylmethyl)-3-oxopropyl]-4-(2-oxopiperidin-1-yl)benzamide
181.	*N*-[3-[(5-chloropyridin-2-yl)amino]-3-oxo-1-(pyrrolidin-1-ylmethyl)propyl]-4-(2-oxopiperidin-1-yl)benzamide
182.	*N*-{3-[(5-chloropyridin-2-yl)amino]-3-oxo-1-[(2-oxopyrrolidin-1-

	yl)methyl]propyl}-4-(2-oxopiperidin-1-yl)benzamide
183.	*N*-{3-[(4-chlorophenyl)amino]-2-methyl-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
184.	*N*-{3-[(4-chlorophenyl)amino]-3-oxo-2-phenylpropyl}-4-(2-oxopiperidin-1-yl)benzamide
185.	*N*-{2-benzyl-3-[(4-chlorophenyl)amino]-3-oxopropyl}-4-(2-oxopiperidin-1-yl)benzamide
186.	5-chloro-*N*-(2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}ethyl)thiophene-2-carboxamide
187.	5-chloro-*N*-(2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
188.	5-chloro-*N*-(2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}-2-phenylethyl)thiophene-2-carboxamide
189.	5-chloro-*N*-(2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}-3-phenylpropyl)thiophene-2-carboxamide
190.	3-{[(5-chloro-2-thienyl)carbonyl]amino}-*N*-[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]alanine
191.	4-{[(5-chloro-2-thienyl)carbonyl]amino}-3-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}butanoic acid
192.	5-{[(5-chloro-2-thienyl)carbonyl]amino}-4-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}pentanoic acid
193.	*N*-(3-amino-2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}propyl)-5-chlorothiophene-2-carboxamide
194.	5-chloro-*N*-(3-(methylamino)-2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
195.	5-chloro-*N*-(3-(dimethylamino)-2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
196.	5-chloro-*N*-(3-[[2-(dimethylamino)ethyl](methyl)amino]-2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
197.	5-chloro-*N*-(3-[methyl(2-morpholin-4-ylethyl)amino]-2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
198.	5-chloro-*N*-(3-[[2-(1,1-dioxidothiomorpholin-4-yl)ethyl](methyl)amino]-2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
199.	5-chloro-*N*-(3-[2-(1,1-dioxidothiomorpholin-4-yl)ethoxy]-2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
200.	5-chloro-*N*-(3-(2-morpholin-4-ylethoxy)-2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
201.	5-chloro-*N*-(3-[2-(2-oxopiperidin-1-yl)ethoxy]-2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
202.	5-chloro-*N*-(1-methyl-2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}ethyl)thiophene-2-carboxamide
203.	5-chloro-*N*-(2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}-1-

	phenylethyl)thiophene-2-carboxamide
204.	*N*-(1-benzyl-2-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}ethyl)-5-chlorothiophene-2-carboxamide
205.	3-{[(5-chloro-2-thienyl)carbonyl]amino}-4-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}butanoic acid
206.	*N*-[(5-chloro-2-thienyl)carbonyl]-3-{[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}alanine
207.	*N*-[2-amino-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]-5-chlorothiophene-2-carboxamide
208.	5-chloro-*N*-[2-(methylamino)-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
209.	5-chloro-*N*-[2-(dimethylamino)-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
210.	*N*-[2-[acetyl(methyl)amino]-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]-5-chlorothiophene-2-carboxamide
211.	5-chloro-*N*-[2-[methyl(methylsulfonyl)amino]-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
212.	5-chloro-*N*-[2-hydroxy-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
213.	5-chloro-*N*-[2-methoxy-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
214.	5-chloro-*N*-[2-[2-(dimethylamino)ethoxy]-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
215.	5-chloro-*N*-[2-(2-morpholin-4-ylethoxy)-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
216.	5-chloro-*N*-[2-[2-(1,1-dioxidothiomorpholin-4-yl)ethoxy]-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
217.	5-chloro-*N*-[2-[2-(4-methylpiperazin-1-yl)ethoxy]-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
218.	5-chloro-*N*-[2-{methyl[2-(4-methylpiperazin-1-yl)ethyl]amino}-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
219.	5-chloro-*N*-[2-[methyl(2-morpholin-4-ylethyl)amino]-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
220.	5-chloro-*N*-[2-[[2-(1,1-dioxidothiomorpholin-4-yl)ethyl](methyl)amino]-1-({[4-(2-oxopyridin-1(2*H*)-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
221.	5-chloro-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}ethyl)thiophene-2-carboxamide
222.	5-chloro-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
223.	5-chloro-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}-2-phenylethyl)thiophene-2-carboxamide

224.	5-chloro-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}-3-phenylpropyl)thiophene-2-carboxamide
225.	3-{[(5-chloro-2-thienyl)carbonyl]amino}-*N*-[4-(2-oxopiperidin-1-yl)benzoyl]alanine
226.	4-{[(5-chloro-2-thienyl)carbonyl]amino}-3-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}butanoic acid
227.	5-{[(5-chloro-2-thienyl)carbonyl]amino}-4-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}pentanoic acid
228.	*N*-(3-amino-2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}propyl)-5-chlorothiophene-2-carboxamide
229.	5-chloro-*N*-(3-(methylamino)-2-{[4-(2-oxopiperidin-1-yl) benzoyl]amino}propyl)thiophene-2-carboxamide
230.	5-chloro-*N*-(3-(dimethylamino)-2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
231.	5-chloro-*N*-(3-[[2-(dimethylamino)ethyl](methyl)amino]-2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
232.	5-chloro-*N*-(3-[methyl(2-morpholin-4-ylethyl)amino]-2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
233.	5-chloro-*N*-(3-[[2-(1,1-dioxidothiomorpholin-4-yl)ethyl](methyl)amino]-2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
234.	5-chloro-*N*-(3-[2-(1,1-dioxidothiomorpholin-4-yl)ethoxy]-2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
235.	5-chloro-*N*-(3-(2-morpholin-4-ylethoxy)-2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
236.	5-chloro-*N*-(3-[2-(2-oxopiperidin-1-yl)ethoxy]-2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}propyl)thiophene-2-carboxamide
237.	5-chloro-*N*-(1-methyl-2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}ethyl)thiophene-2-carboxamide
238.	5-chloro-*N*-(2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}-1-phenylethyl)thiophene-2-carboxamide
239.	*N*-(1-benzyl-2-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}ethyl)-5-chlorothiophene-2-carboxamide
240.	3-{[(5-chloro-2-thienyl)carbonyl]amino}-4-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}butanoic acid
241.	*N*-[(5-chloro-2-thienyl)carbonyl]-3-{[4-(2-oxopiperidin-1-yl)benzoyl]amino}alanine
242.	*N*-[2-amino-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]-5-chlorothiophene-2-carboxamide
243.	5-chloro-*N*-[2-(methylamino)-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
244.	5-chloro-*N*-[2-(dimethylamino)-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide

245.	*N*-[2-[acetyl(methyl)amino]-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]-5-chlorothiophene-2-carboxamide
246.	5-chloro-*N*-[2-[methyl(methylsulfonyl)amino]-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
247.	5-chloro-*N*-[2-hydroxy-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
248.	5-chloro-*N*-[2-methoxy-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
249.	5-chloro-*N*-[2-[2-(dimethylamino)ethoxy]-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
250.	5-chloro-*N*-[2-(2-morpholin-4-ylethoxy)-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
251.	5-chloro-*N*-[2-[2-(1,1-dioxidothiomorpholin-4-yl)ethoxy]-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
252.	5-chloro-*N*-[2-[2-(4-methylpiperazin-1-yl)ethoxy]-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
253.	5-chloro-*N*-[2-{methyl[2-(4-methylpiperazin-1-yl)ethyl]amino}-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
254.	5-chloro-*N*-[2-[methyl(2-morpholin-4-ylethyl)amino]-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
255.	5-chloro-*N*-[2-[[2-(1,1-dioxidothiomorpholin-4-yl)ethyl](methyl)amino]-1-({[4-(2-oxopiperidin-1-yl)benzoyl]amino}methyl)ethyl]thiophene-2-carboxamide
256.	*N*-(4-chlorophenyl)-*N'*-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]succinamide
257.	*N*-(5-chloropyridin-2-yl)-*N'*-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]succinamide
258.	*N*-(5-chloropyridin-2-yl)-*N'*-[4-(2-oxopiperidin-1-yl)phenyl]succinamide
259.	*N*-(4-chlorophenyl)-*N'*-[4-(2-oxopiperidin-1-yl)phenyl]succinamide
260.	2-({[(4-chlorophenyl)amino]carbonyl}amino)-*N*-[4-(2-oxopiperidin-1-yl)phenyl]-2-phenylacetamide
261.	2-({[(5-chloropyridin-2-yl)amino]carbonyl}amino)-*N*-[4-(2-oxopiperidin-1-yl)phenyl]-2-phenylacetamide
262.	3-chloro-*N*-(2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-phenylethyl)-1*H*-indole-6-carboxamide
263.	3-chloro-*N*-(1-(2-fluorophenyl)-2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
264.	3-chloro-*N*-(2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}-1-phenylethyl)-1*H*-indole-6-carboxamide
265.	3-chloro-*N*-(1-(2-chlorophenyl)-2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
266.	3-chloro-*N*-(1-(2-fluorophenyl)-2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
267.	3-chloro-*N*-(1-(2-methoxyphenyl)-2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-

	yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
268.	*N*-(1-[3-(aminocarbonyl)phenyl]-2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}ethyl)-3-chloro-1*H*-indole-6-carboxamide
269.	3-chloro-*N*-(1-[3-(methylsulfonyl)phenyl]-2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
270.	3-chloro-*N*-(1-(2-methylphenyl)-2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
271.	3-chloro-*N*-(2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}-1-pyridin-2-ylethyl)-1*H*-indole-6-carboxamide
272.	3-chloro-*N*-(2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}-1-pyridin-3-ylethyl)-1*H*-indole-6-carboxamide
273.	3-chloro-*N*-(2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}-1-pyridin-4-ylethyl)-1*H*-indole-6-carboxamide
274.	3-chloro-*N*-(1-(2-cyanophenyl)-2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
275.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}-1-(3-thienyl)ethyl]-1*H*-indole-6-carboxamide
276.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}-1-(2-thienyl)ethyl]-1*H*-indole-6-carboxamide
277.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}-1-(4-thienyl)ethyl]-1*H*-indole-6-carboxamide
278.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}-1-(1,3-thiazol-4-yl)ethyl]-1*H*-indole-6-carboxamide
279.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}-1-(1,3-thiazol-5-yl)ethyl]-1*H*-indole-6-carboxamide
280.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}-1-(1,3-thiazol-2-yl)ethyl]-1*H*-indole-6-carboxamide
281.	3-chloro-*N*-(1-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
282.	3-chloro-*N*-(1-(2-naphthyl)-2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
283.	3-chloro-*N*-(1-(1-naphthyl)-2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
284.	*N*-(1-(1-benzothien-2-yl)-2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}ethyl)-3-chloro-1*H*-indole-6-carboxamide
285.	3-chloro-*N*-(2-oxo-2-{[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}-1-quinolin-4-ylethyl)-1*H*-indole-6-carboxamide
286.	3-chloro-*N*-(2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-phenylethyl)-1*H*-indole-6-carboxamide
287.	3-chloro-*N*-(1-(2-chlorophenyl)-2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
288.	3-chloro-*N*-(1-(2-fluorophenyl)-2-oxo-2-{[4-(2-oxopiperidin-1-

	yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
289.	3-chloro-*N*-(1-(2-methoxyphenyl)-2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
290.	*N*-(1-[3-(aminocarbonyl)phenyl]-2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}ethyl)-3-chloro-1*H*-indole-6-carboxamide
291.	3-chloro-*N*-(1-[3-(methylsulfonyl)phenyl]-2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
292.	3-chloro-*N*-(1-(2-methylphenyl)-2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
293.	3-chloro-*N*-(2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-pyridin-2-ylethyl)-1*H*-indole-6-carboxamide
294.	3-chloro-*N*-(2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-pyridin-3-ylethyl)-1*H*-indole-6-carboxamide
295.	3-chloro-*N*-(2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-pyridin-4-ylethyl)-1*H*-indole-6-carboxamide
296.	3-chloro-*N*-(1-(2-cyanophenyl)-2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
297.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-(3-thienyl)ethyl]-1*H*-indole-6-carboxamide
298.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-(2-thienyl)ethyl]-1*H*-indole-6-carboxamide
299.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-(4-thienyl)ethyl]-1*H*-indole-6-carboxamide
300.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-(1,3-thiazol-4-yl)ethyl]-1*H*-indole-6-carboxamide
301.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-(1,3-thiazol-5-yl)ethyl]-1*H*-indole-6-carboxamide
302.	3-chloro-*N*-[2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-(1,3-thiazol-2-yl)ethyl]-1*H*-indole-6-carboxamide
303.	3-chloro-*N*-(1-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
304.	3-chloro-*N*-(1-(2-naphthyl)-2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
305.	3-chloro-*N*-(1-(1-naphthyl)-2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}ethyl)-1*H*-indole-6-carboxamide
306.	*N*-(1-(1-benzothien-2-yl)-2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}ethyl)-3-chloro-1*H*-indole-6-carboxamide
307.	3-chloro-*N*-(2-oxo-2-{[4-(2-oxopiperidin-1-yl)phenyl]amino}-1-quinolin-4-ylethyl)-1*H*-indole-6-carboxamide
308.	2-(1-benzothien-2-yl)-2-({[(4-chlorophenyl)amino]carbonyl}amino)-*N*-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]acetamide
309.	2-(1-benzothien-2-yl)-2-({[(4-chlorophenyl)amino]carbonyl}amino)-*N*-[4-(2-

	oxopiperidin-1-yl)phenyl]acetamide
310.	*N*-[(3-chloro-1*H*-indol-6-yl)carbonyl]-*N*-[4-(2-oxopiperidin-1-yl)phenyl]phenylalaninamide
311.	N^2-[(3-chloro-1*H*-indol-6-yl)carbonyl]-N^1-[4-(2-oxopiperidin-1-yl)phenyl]aspartamide
312.	N^2-[(3-chloro-1*H*-indol-6-yl)carbonyl]-N^1-[4-(2-oxopiperidin-1-yl)phenyl]-□-asparagine
313.	2-{[(3-chloro-1*H*-indol-6-yl)carbonyl]amino}-*N*-[4-(2-oxopiperidin-1-yl)phenyl]malonamide
314.	N^2-[(3-chloro-1*H*-indol-6-yl)carbonyl]-N^1-[4-(2-oxopiperidin-1-yl)phenyl]glutamamide
315.	3-chloro-*N*-[3-(methylsulfonyl)-1-({[4-(2-oxopiperidin-1-yl)phenyl]amino}carbonyl)propyl]-1*H*-indole-6-carboxamide
316.	3-chloro-*N*-[1-({[4-(2-oxopiperidin-1-yl)phenyl]amino}carbonyl)-3-phenylpropyl]-1*H*-indole-6-carboxamide
317.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopiperidin-1-yl)phenyl]norvalinamide
318.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopiperidin-1-yl)phenyl]alaninamide
319.	2-({[(4-chlorophenyl)amino]carbonyl}amino)-*N*-[4-(2-oxopiperidin-1-yl)phenyl]butanamide
320.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopiperidin-1-yl)phenyl]valinamide
321.	*N*-{[(4-chlorophenyl)amino]carbonyl}-*N*-[4-(2-oxopiperidin-1-yl)phenyl]phenylalaninamide
322.	2-({[(4-chlorophenyl)amino]carbonyl}amino)-*N*-[4-(2-oxopiperidin-1-yl)phenyl]-4-phenylbutanamide
323.	2-({[(4-chlorophenyl)amino]carbonyl}amino)-*N*-[4-(2-oxopiperidin-1-yl)phenyl]malonamide
324.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopiperidin-1-yl)phenyl]aspartamide
325.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopiperidin-1-yl)phenyl]glutamamide
326.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopiperidin-1-yl)phenyl]lysinamide
327.	2-({[(4-chlorophenyl)amino]carbonyl}amino)-4-(methylsulfonyl)-*N*-[4-(2-oxopiperidin-1-yl)phenyl]butanamide
328.	2-({[(4-chlorophenyl)amino]carbonyl}amino)-4-(methylsulfonyl)-*N*-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]butanamide
329.	*N*-[(3-chloro-1*H*-indol-6-yl)carbonyl]-*N*-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]phenylalaninamide

330.	N^2-[(3-chloro-1*H*-indol-6-yl)carbonyl]-N^1-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]aspartamide
331.	N^2-[(3-chloro-1*H*-indol-6-yl)carbonyl]-N^1-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]-□-asparagine
332.	2-{[(3-chloro-1*H*-indol-6-yl)carbonyl]amino}-*N*-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]malonamide
333.	N^2-[(3-chloro-1*H*-indol-6-yl)carbonyl]-N^1-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]glutamamide
334.	3-chloro-*N*-[3-(methylsulfonyl)-1-({[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}carbonyl)propyl]-1*H*-indole-6-carboxamide
335.	3-chloro-*N*-[1-({[4-(2-oxopyridin-1(2*H*)-yl)phenyl]amino}carbonyl)-3-phenylpropyl]-1*H*-indole-6-carboxamide
336.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]norvalinamide
337.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]alaninamide
338.	2-({[(4-chlorophenyl)amino]carbonyl}amino)-*N*-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]butanamide
339.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]valinamide
340.	*N*-{[(4-chlorophenyl)amino]carbonyl}-*N*-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]phenylalaninamide
341.	2-({[(4-chlorophenyl)amino]carbonyl}amino)-*N*-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]-4-phenylbutanamide
342.	2-({[(4-chlorophenyl)amino]carbonyl}amino)-*N*-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]malonamide
343.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]aspartamide
344.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]glutamamide
345.	N^2-{[(4-chlorophenyl)amino]carbonyl}-N^1-[4-(2-oxopyridin-1(2*H*)-yl)phenyl]lysinamide
346.	N-[3-(4-Chloro-cyclopenta-1,3-dienesulfonylamino)-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
347.	N-[3-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
348.	N-[3-(4-Chloro-cyclopenta-1,3-dienesulfonylamino)-3-oxo-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
349.	N-[3-(4-Chloro-cyclopenta-1,3-dienesulfonylamino)-3-oxo-propyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
350.	N-[3-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonylamino)-3-oxo-propyl]-4-(2-

	oxo-2H-pyridin-1-yl)-benzamide
351.	N-[2-(6-Chloro-naphthalene-2-sulfonylamino)-2-oxo-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
352.	N-[2-(6-Chloro-naphthalene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
353.	N-[2-(6-Chloro-naphthalene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
354.	N-[2-(6-Chloro-naphthalene-2-sulfonylamino)-2-oxo-ethyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
355.	N-[3-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
356.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
357.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
358.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
359.	N-[3-(4-Chloro-benzenesulfonylamino)-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
360.	N-[3-(4-Chloro-benzenesulfonylamino)-3-oxo-propyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
361.	N-[2-(6-Chloro-1H-indole-2-sulfonylamino)-2-oxo-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
362.	N-[1-(6-Chloro-naphthalene-2-sulfonylaminocarbonyl)-2-methyl-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
363.	N-[2-(6-Chloro-naphthalene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
364.	N-[2-(6-Chloro-naphthalene-2-sulfonylamino)-2-oxo-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
365.	N-[3-(5-Chloro-pyridine-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
366.	N-[1-(6-Chloro-1H-indole-2-sulfonylaminocarbonyl)-2-methyl-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
367.	N-[1-(6-Chloro-naphthalene-2-sulfonylaminocarbonyl)-2-methyl-butyl]-4-(2-oxo-piperidin-1-yl)-benzamide
368.	N-[2-(5-Chloro-thiophene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
369.	N-[2-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
370.	N-[2-(5-Chloro-thiophene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
371.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-

	oxo-piperidin-1-yl)-benzamide
372.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
373.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
374.	N-[3-(4-Chloro-benzenesulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
375.	N-[3-(4-Chloro-benzenesulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
376.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-3-oxo-2-phenyl-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
377.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-3-oxo-2-phenyl-propyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
378.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-3-oxo-2-phenyl-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
379.	N-[3-(4-Chloro-benzenesulfonylamino)-3-oxo-2-phenyl-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
380.	N-[3-(5-Chloro-pyridine-2-sulfonylamino)-3-oxo-2-phenyl-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
381.	N-[2-(6-Chloro-1H-indole-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
382.	N-[2-(6-Chloro-naphthalene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
383.	N-[2-(5-Chloro-thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
384.	N-[2-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
385.	N-[2-(5-Chloro-thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
386.	N-[2-(4-Chloro-benzenesulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
387.	N-[2-(5-Chloro-pyridine-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
388.	N-[2-(4-Chloro-benzenesulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
389.	N-[2-(5-Chloro-pyridine-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
390.	N-[2-(4-Chloro-benzenesulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
391.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-2,2-dimethyl-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
392.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-2,2-dimethyl-3-oxo-propyl]-4-

	(2-oxo-2H-pyridin-1-yl)-benzamide
393.	N-[3-(6-Chloro-1H-indole-2-sulfonylamino)-2,2-dimethyl-3-oxo-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
394.	N-[3-(4-Chloro-benzenesulfonylamino)-2,2-dimethyl-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
395.	N-[3-(5-Chloro-pyridine-2-sulfonylamino)-2,2-dimethyl-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
396.	N-[3-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
397.	N-[3-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
398.	N-[3-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
399.	N-[2-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
400.	N-[2-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
401.	N-[2-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
402.	N-[3-(6-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
403.	N-[3-(6-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
404.	N-[3-(6-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
405.	N-[2-(6-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
406.	N-[2-(6-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
407.	N-[2-(6-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
408.	N-[2-Methyl-3-(6-methyl-benzo[b]thiophene-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
409.	N-[2-Methyl-1-(6-methyl-benzo[b]thiophene-2-sulfonylaminocarbonyl)-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
410.	N-[2-Methyl-3-(6-methyl-benzo[b]thiophene-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
411.	N-[2-Methyl-1-(6-methyl-benzo[b]thiophene-2-sulfonylaminocarbonyl)-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
412.	N-[2-Methyl-3-(6-methyl-benzo[b]thiophene-2-sulfonylamino)-3-oxo-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
413.	N-[2-Methyl-1-(6-methyl-benzo[b]thiophene-2-sulfonylaminocarbonyl)-

	propyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
414.	N-[3-(3,6-Dimethyl-benzo[b]thiophene-2-sulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
415.	N-[1-(3,6-Dimethyl-benzo[b]thiophene-2-sulfonylaminocarbonyl)-2-methyl-propyl]-4-(2-oxo-piperidin-1-yl)-benzamide
416.	N-[2-(3,6-Dimethyl-benzo[b]thiophene-2-sulfonylaminocarbonyl)-butyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
417.	N-[1-(3,6-Dimethyl-benzo[b]thiophene-2-sulfonylaminocarbonyl)-2-methyl-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
418.	N-[3-(6-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-2-methyl-3-oxo-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
419.	N-[2-(3,6-Dimethyl-benzo[b]thiophene-2-sulfonylamino)-1-methyl-2-oxo-ethyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
420.	N-[2-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
421.	N-[2-(6-Methyl-benzo[b]thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
422.	N-[2-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
423.	N-[2-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
424.	N-[2-(6-Methyl-benzo[b]thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
425.	N-[2-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
426.	N-[2-(3,6-Dimethyl-benzo[b]thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-piperidin-1-yl)-benzamide
427.	N-[2-(6-Chloro-benzo[b]thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
428.	N-[2-(3,6-Dimethyl-benzo[b]thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
429.	N-[2-(3,6-Dimethyl-benzo[b]thiophene-2-sulfonylamino)-2-oxo-1-phenyl-ethyl]-4-(2-oxo-2H-pyridin-1-yl)-benzamide
430.	N-(4-Chloro-phenyl)-N'-{2-oxo-2-[4-(2-oxo-2H-pyrazin-1-yl)-piperidin-1-yl]-1-phenyl-ethyl}-oxalamide
431.	5-Chloro-thiophene-2-carboxylic acid [2-oxo-2-(2-oxo-3',4',5',6'-tetrahydro-2H,2'H-[1,4']bipyridinyl-1'-yl)-1-phenyl-ethyl]-amide
432.	5-Chloro-thiophene-2-carboxylic acid {2-oxo-2-[4-(2-oxo-2H-pyrazin-1-yl)-piperidin-1-yl]-1-phenyl-ethyl}-amide
433.	2-Oxo-3',4',5',6'-tetrahydro-2H,2'H-[1,4']bipyridinyl-1'-carboxylic acid {2-[(5-chloro-thiophene-2-carbonyl)-amino]-ethyl}-amide
434.	4-(2-Oxo-2H-pyrazin-1-yl)-piperidine-1-carboxylic acid {2-[(5-chloro-

	thiophene-2-carbonyl)-amino]-ethyl}-amide
435.	5-Chloro-thiophene-2-carboxylic acid {[4-(2-oxo-2H-pyrazin-1-yl)-phenylcarbamoyl]-phenyl-methyl}-amide
436.	5-Chloro-thiophene-2-carboxylic acid {[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]-phenyl-methyl}-amide
437.	5-Chloro-thiophene-2-carboxylic acid {[4-(2-oxo-[1,3]oxazinan-3-yl)-phenylcarbamoyl]-phenyl-methyl}-amide
438.	5-Chloro-thiophene-2-carboxylic acid {3-(1-methyl-1H-imidazol-2-yl)-1-[4-(2-oxo-2H-pyridin-1-yl)-phenylcarbamoyl]-propyl}-amide
439.	5-Chloro-thiophene-2-carboxylic acid [[4-(2-oxo-2H-pyridin-1-yl)-phenylcarbamoyl]-(tetrahydro-pyran-4-yl)-methyl]-amide
440.	5-Chloro-thiophene-2-carboxylic acid [[4-(2-oxo-2H-pyrazin-1-yl)-phenylcarbamoyl]-(tetrahydro-pyran-4-yl)-methyl]-amide
441.	5-Chloro-thiophene-2-carboxylic acid {2-[4-(2-oxo-2H-pyrazin-1-yl)-benzoylamino]-ethyl}-amide
442.	5-Chloro-thiophene-2-carboxylic acid {2-[4-(2-oxo-2H-pyrazin-1-yl)-benzoylamino]-propyl}-amide
443.	5-Chloro-thiophene-2-carboxylic acid (3-methoxy-1-{[4-(2-oxo-2H-pyrazin-1-yl)-benzoylamino]-methyl}-propyl)-amide
444.	5-Chloro-thiophene-2-carboxylic acid {4-methoxy-2-[4-(2-oxo-2H-pyrazin-1-yl)-benzoylamino]-butyl}-amide
445.	5-Chloro-thiophene-2-carboxylic acid {3-(1-methyl-1H-imidazol-2-yl)-2-[4-(2-oxo-2H-pyridin-1-yl)-benzoylamino]-propyl}-amide
446.	5-Chloro-thiophene-2-carboxylic acid {1-(1-methyl-1H-imidazol-2-ylmethyl)-2-[4-(2-oxo-2H-pyridin-1-yl)-benzoylamino]-ethyl}-amide
447.	5-Chloro-thiophene-2-carboxylic acid {2-[4-(2-oxo-2H-pyridin-1-yl)-benzoylamino]-2-phenyl-ethyl}-amide
448.	5-Chloro-thiophene-2-carboxylic acid {2-[4-(2-oxo-2H-pyridin-1-yl)-benzoylamino]-1-phenyl-ethyl}-amide
449.	5-Chloro-thiophene-2-carboxylic acid {2-[4-(2-oxo-2H-pyrazin-1-yl)-benzoylamino]-2-phenyl-ethyl}-amide
450.	5-Chloro-thiophene-2-carboxylic acid {1-methyl-2-[4-(2-oxo-2H-pyrazin-1-yl)-benzoylamino]-propyl}-amide
451.	N-[2-(4-Chloro-phenylcarbamoyl)-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
452.	N-[2-(4-Chloro-phenylcarbamoyl)-1-methyl-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
453.	N-[2-(4-Chloro-phenylcarbamoyl)-propyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide
454.	N-[2-(5-Chloro-pyridin-2-ylcarbamoyl)-1-methyl-ethyl]-4-(2-oxo-2H-pyrazin-1-yl)-benzamide

Numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise that as specifically described herein.